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HÆMOLYTIC SUBSTANCES IN HEATED MILK AND IN MILK CULTURES OF BACTERIUM WELCHII.

By William W. Ford and Joseph H. Lawrence.

(From the Bacteriological Laboratory, The Johns Hopkins University.)

Milk heated to temperatures above 60° C., in which the non-spore-bearing bacteria are destroyed, decomposes from the multiplication of the aërobic and anaërobic spore-bearing bacteria which are always present. In a large proportion of the samples of milk obtained from the Baltimore markets an explosive reaction occurs which is usually due to the multiplication of *Bacterium welchii*[1] (*B. aerogenes capsulatus*). Sterile milk inoculated with this organism in pure culture shows a similar explosive reaction but the liquefaction observed in the samples of heated market milk is lacking. *Bacterium welchii* does not peptonise casein and the liquefaction found in the market milk must be due to other bacteria, probably to the aërobic spore-bearers.

The whey from the decomposed market milk sometimes has poisonous properties. If it be injected intravenously into rabbits these animals occasionally die with some of the symptoms of protein intoxication. Neutralization of the whey, which is often highly acid, at times does away completely with the toxic property of the milk but not in all instances. The subcutaneous injection of the whey may also be toxic to rabbits which show an œdema at the site of inoculation, a fluid tinged with hæmoglobin in the peritoneal cavity and a hæmoglobin-stained urine. Neutralized whey is sometimes without this action upon animals. In other cases, however, the animals succumb in a few days and at autopsy show a subcutaneous œdema, a clear red fluid in the peritoneal cavity and a urine tinged with hæmoglobin. These findings all point to a hæmolytic intoxication and suggest that the decomposed milk may owe its poisonous properties in part at least to hæmolytic substances in addition to the excessive acidity. The poisonous action of heated and decomposed milk as well as the poisonous action of milk inoculated with pure cultures of *Bacterium welchii* is now being made the subject of further study. In order to elucidate it, however, it was first necessary to investigate the hæmolytic action of the whey from decomposed milk and from pure milk cultures of this organism. The results of this work seemed of sufficient interest to report at the present time.

Hæmolytic Substances in Decomposed Market Milk.

Samples of Baltimore market milk heated to 85° C. for 15-20 minutes and incubated at 22° C. or at 37° C. for 24-48 hours explode violently with or without a subsequent peptonization. The fluid from such decomposed milk after filtration has hæmolytic properties for a variety of blood corpuscles. The bloods of rabbits, guinea-pigs, chickens and pigs are all sensitive and in about the same degree. The following table shows the hæmolytic activity of a typical sample:

TABLE I.

Hæmolytic Action of Fluid from Decomposed Milk.

Sample quantity.		Rabbit's blood, 5 % suspension.		Hæmolysis.
1.00 c. c.	+	1 c. c.	=	Complete.
0.75 c. c.	+	1 c. c.	=	"
0.50 c. c.	+	1 c. c.	=	"
0.25 c. c.	+	1 c. c.	=	"
0.10 c. c.	+	1 c. c.	=	Partial.
0.05 c. c.	+	1 c. c.	=	Negative.

All tubes made up to a total bulk of 3 c. c.
Control 1 c. c. NaCl 0.75% negative.

In this sample complete hæmolysis of 1 c. c. of 5 per cent rabbit's blood was produced by 0.25 c. c. of the filtered whey. Other samples of milk treated in the same way were also hæmolytic. The strength of the hæmolysin varied somewhat with the character of the milk and somewhat from day to day. It usually began to appear within the first 24-48 hours, increased slowly and reached its maximal intensity on the sixth or seventh day, after which it remained stationary for a time and then slowly deteriorated. The most active hæmolysins found were those in which complete solution of 1 c. c. of 5 per cent rabbit's blood was produced by 0.05 c. c. quantities equaling a dilution of 1-20. These were exceptional, however, the usual strength being 0.1 to 0.25 c. c. The hæmolysins proved fairly constant in the samples of milk treated in this way. The following table illustrates the strength of the hæmolysins found in a series of samples examined on one day:

TABLE II.

Hæmolysins in Samples of Decomposed Market Milk.

Sample.	Quantity necessary to give complete hæmolysis of 1 c. c. 5 % rabbit's blood.
C.	0.75
N.	0.5
N.	0.75
S.	0.5
H.	0.1
W.	0.25

All the specimens gave cultures of *Bacterium welchii* on rabbit inoculation.

The hæmolysins in these milks were not typical, however, since with the lower dilutions the blood took on a dark-brown color like that due to methæmoglobin. In the higher dilutions the reaction was more characteristic, the tubes showing clear solutions tinged red with hæmoglobin. On testing with litmus the whey was found to be acid in reaction. If this acidity was carefully neutralized by sodium bicarbonate and the neutralized whey then tested, beautiful clear hæmolysins were found like those produced by other hæmolytic agents. This is shown in the following table which gives the reactions of two characteristic samples. The hæmolytic action of the acid material is slightly greater than that of the neutralized.

TABLE III.

Action of Whey on Rabbit's Corpuscles Before and After Neutralization.

Sample.	Quantity used with 1 c. c. 5 % rabbit's blood.				
	0.1 c.c.	0.075 c.c.	0.05 c.c.	0.025 c.c.	0.01 c.c.
H. before neutralization	+ +	+ +	+ +	+	Trace
H. after neutralization	+ +	+ +	+ +	+	0
W. before neutralization	+ +	+ +	+ +	+	Trace
W. after neutralization	+ +	+ +	+ +	+	0

Control NaCl negative.
+ + = Complete hæmolysis.
+ = Partial hæmolysis.
0 = No hæmolysis.

The hæmolytic substances in this decomposed milk, therefore, are not the result of the acids (butyric and lactic) found in such milk, since they are present after neutralization. They react like true bacterial hæmolysins. This was borne out by a study of the thermal death-point, which lies between 55° C. and 60° C., as can be seen from the following table:

TABLE IV.

Thermal Death-Point of Hæmolysins in Whey of Decomposed Milk.

Sample.	Quantity used with 1 c. c. of 5 % rabbit's blood.			
	1.0 c. c.	0.5 c. c.	0.25 c. c.	0.1 c. c.
Neutralized raw	+ +	+ +	+ +	+ +
Heated to 55° C. ½ hour	+	+	+	+
Heated to 60° C. ½ hour	0	0	0	0

Control NaCl negative.
+ + = Complete hæmolysis.
+ = Partial hæmolysis.
0 = No hæmolysis.

The hæmolysin is thus thermolabile, being weakened by exposure to 55° C. one-half hour and destroyed at temperatures between 55° C. and 60° C. This thermal death-point corresponds to the thermal death-points of bacterial hæmolysins in general, which lie between 55° C. and 60° C. In addition to being thermolabile bacterial hæmolysins are usually precipitable by reagents which throw down proteins such as ethyl alcohol and are sensitive to the digestive action of pepsin and pancreatin. The hæmolysin in milk can be precipitated by ethyl alcohol as is shown by the following protocol:

Hæmolysin in Decomposed Milk Precipitable by Ethyl Alcohol.

A small quantity of whey from sample of decomposed market milk H., which gave complete hæmolysis of 1 c. c. 5 per cent rabbit's blood in a dilution of 1-20, was treated with several times its volume of 95 per cent ethyl alcohol. A fine, flocculent precipitate was obtained. This was collected on filter paper, dried and taken up in 0.75 per cent NaCl. On testing with rabbit's blood it was found to be powerfully hæmolytic. The filtrate was without action on corpuscles.

The hæmolysin was also sensitive to the action of pepsin and pancreatin. When mixed with these substances in dried

powder form, placed at 37° C. for 24 hours and then tested upon blood corpuscles, it is without blood-laking properties. This is shown in the following table:

TABLE V.

ACTION OF PEPSIN AND PANCREATIN ON HÆMOLYSIN IN DECOMPOSED MILK.

Specimen.	Quantity used for hæmolysis of 1 c. c. of 5% rabbit's blood.		
	1 c. c.	0.5 c. c.	0.25 c. c.
H.	+ +	+ +	+ +
H. plus pepsin	0	0	0
H. plus pancreatin	0	0	0
Pepsin in 0.75% NaCl	0	0	0
Pancreatin in 0.75% NaCl.	0	0	0

+ + = Complete hæmolysis.
0 = No hæmolysis.

Heated market milk allowed to decompose thus contains an hæmolysin which may be classed as a true bacterial hæmolysin because of its thermolability, its precipitability by alcohol, its sensitiveness to pepsin and pancreatin. As has been shown by previous investigations,[2] such milk is heavily infected by aërobic spore-bearing bacteria belonging to the groups of *Bacillus subtilis, Bacillus mesentericus, Bacillus cereus* and *Bacillus albolactus.* These organisms are devoid of hæmolytic activity as far as we know. As noted above, specimens of market milk in Baltimore, which when heated to 85° C. for 15-20 minutes decompose violently, always contain *Bacterium welchii.* This organism has well marked blood-laking properties, as is shown especially by the investigations of Herter,[3] McCampbell,[4] Simonds[5] and others, and the hæmolysin in this decomposed milk may well be attributed to the development of this species. It has furthermore been shown that the lactic acid bacteria in raw milk inhibit the development of the gas bacillus. Raw milk allowed to clot does not decompose violently and the whey does not contain *Bacterium welchii* under ordinary circumstances. If the hæmolysin in the heated and decomposed milk is to be attributed to the gas bacillus it should not be present in raw soured milk. This point was tested by taking a series of six milks, and dividing them each into two lots. One lot was incubated at 37° C. for 48 hours and then kept at room temperature. The highly acid whey from each was neutralized by sodium bicarbonate and tested upon blood corpuscles at the end of three days and again at the end of 14 days. It was devoid of hæmolytic activity on all occasions. The other lot of six samples was heated to 85° C. for 15 minutes, incubated for 24 hours at 37° C. These samples exploded violently and all but one of them showed true hæmolysins after the acidity was neutralized. Hæmolysins thus develop in milk heated to 85° C. and incubated, while they fail to develop in the same milk when allowed to sour normally. Since such samples of explosive milk always contain actively growing *Bacterium welchii* this organism is further implicated as the source of the hæmolysin. The difference between raw and heated milk is brought out in the following table:

TABLE VI.

ACTION OF WHEY FROM RAW AND HEATED MILK UPON RABBIT'S CORPUSCLES.

Sample.	Quantity used with 1 c. c. rabbit's blood (5 % susp.).				
	1 c. c.	0.75 c. c.	0.5 c. c.	0.25 c. c.	0.1 c. c.
A. raw	0	0	0	0	0
A. heated	+	+	+	0	0
S. raw	0	0	0	0	0
S. heated	+	+.	+	+	0
S. F. raw	0	0	0	0	0
S. F. heated	0	0	0	0	0
A. S. raw	0	0	0	0	0
A. S. heated	+	0	0	0	0
C. raw	0	0	0	0	0
C. heated	+	0	0	0	0
W. raw	0	0	0	0	0
W. heated	+	0	0	0	0

From this table it may be seen that five of the six samples of heated milk showed hæmolytic substances varying in strength from 1 c. c. to 0.25 c. c., but that all the samples of whey from the raw milk were devoid of hæmolysins. The hæmolysin found in decomposed market milk can thus be attributed to the development of *Bacterium welchii,* which is known to produce blood-laking substances, provided its reactions are the same as those of the hæmolysin produced by this species. The hæmolysin of the gas bacillus is not usually regarded as a true bacterial hæmolysin but is attributed to the various acids produced in culture media by the growth of this organism, particularly to the butyric and lactic acids. Herter was inclined to believe that the hæmolysin was due to the acids because of its resistance to heat, while McCampbell attributed it to butyric acid which he says is hæmolytic in about the same degree as the acid cultures of the organism. It became necessary, therefore, to make a further study of the hæmolytic substances produced by *Bacterium welchii,* particularly in milk cultures.

HÆMOLYSINS IN MILK CULTURES OF BACTERIUM WELCHII.

From one of the flasks of market milk which after heating to 85° C. had been incubated and had shown an explosive reaction, a pure culture of the gas bacillus was obtained by the inoculation of a rabbit by the usual procedure. This organism was a large Gram-positive encapsulated bacillus giving the cultural reactions of *Bacterium welchii.* Two large flasks of milk were inoculated with this strain and incubated for 24 hours. They both showed the characteristic explosive reaction. The whey from each was collected carefully by pipetting it off from the mass of gas-eaten curd, filtered several times through filter paper and finally through a Berkefeld candle. The resulting clear solutions were found to be hæmolytic for rabbit's corpuscles in a dilution of 1-40. In the greater concentrations the tubes took on a dirty-brown color like that of methæmoglobin, suggesting that the hæmolysis was due to acid. After careful neutralization the whey was still hæmolytic to about the same degree as the acid material. The tubes no longer showed the dirty-brown color but were a clear scarlet, characteristic of hæmolysis not due to acid.

The action of the whey from cultures of *Bacterium welchii* before and after neutralization is shown in the following table:

TABLE VII.

HÆMOLYTIC ACTION OF MILK CULTURES OF BACTERIUM WELCHII.

Sample.	Quantity used with 1 c. c. 5 % rabbit's blood.					
	.05 c.c.	.25 c.c.	.01 c.c.	.0075 c.c.	.005 c.c.	.0025 c.c.
A.	+ +	+ +	+	+	Trace	0
A. neutralized.	+ +	+ +	+	+	+	Trace
B.	+ +	+ +	+	+	Trace	0
B. neutralized.	+ +	+ +	+	+	Trace	0

+ + = Complete hæmolysis.
+ = Partial hæmolysis.
0 = No hæmolysis.

NOTE.—The greater concentrations of whey were completely hæmolytic but have not been included in the table.

The hæmolysin in milk cultures of *Bacterium welchii* is thus independent of the acidity of the cultures. In the two samples of the above table it had a strength somewhat greater than that of the hæmolysin found previously in decomposed market milk, being present in 0.025 quantities, a dilution of 1-40. This greater development of hæmolytic activity may be due to the fact that in these flasks the gas bacillus was in pure culture and its growth was not interfered with by other organisms. It appeared usually within the first 24 hours, and in the samples thus far examined seemed to reach its maximal intensity on about the third day. Its appearance in the whey after neutralization of the acids present suggests that it is a true bacterial hæmolysin. This is borne out by a study of the thermal death-point, which lies between 55° C. and 60° C., as is shown in the following table:

TABLE VIII.

THERMAL DEATH-POINT OF HÆMOLYSIN OF BACTERIUM WELCHII.

Sample.	Quantity used to hæmolyse 1 c. c. 5 % rabbit's blood.			
	1 c. c.	0.5 c. c.	0.25 c. c.	0.1 c. c.
B. neutralized	+ +	+ +	+ +	+ +
Heated to 55° C. ½ hour.....	+	+	+	+
Heated to 60° C. ½ hour.....	0	0	0	0

+ + = Complete hæmolysis.
+ = Partial hæmolysis.
0 = No hæmolysis.

The hæmolysin of *Bacterium welchii* corresponds to the true bacterial hæmolysins in other respects. Thus it may be precipitated by ethyl alcohol, as is shown by the following protocol:

HÆMOLYSIN OF BACTERIUM WELCHII PRECIPITABLE BY ETHYL ALCOHOL.

The whey from a milk culture of *Bacterium welchii* was filtered several times through filter paper, then through a Berkefeld candle, neutralized by sodium bicarbonate and when tested upon rabbit's blood was found to have hæmolytic activity in a dilution of 1-40. It was treated with several times its volume of 95 per cent ethyl alcohol. A fine, flocculent precipitate was obtained. This was collected on a filter paper, dried, taken up in 0.75 per cent NaCl and found to be powerfully hæmolytic to rabbit's blood. The filtrate was without action on blood.

The hæmolysin of *Bacterium welchii* is also sensitive to pepsin and pancreatin. Mixed with these substances and placed at 37° C. for 24 hours, active solutions of the hæmolysins lose their blood-laking properties, as is evident from the following table:

TABLE IX.

ACTION OF PEPSIN AND PANCREATIN ON HÆMOLYSIN OF BACTERIUM WELCHII.

Specimen.	Quantity used for hæmolysis of 1 c. c. of 5 % rabbit's blood.		
	1 c. c.	0.5 c. c.	0.25 c. c.
welchii	+ +	+ +	+ +
welchii plus pepsin.....	0	0	0
welchii plus pancreatin	0	0	0
Pancreatin	0	0	0
Pepsin	0	0	0

+ + = Complete hæmolysis.
0 = No hæmolysis.

The hæmolysin in milk cultures of *Bacterium welchii* is thus independent of the acidity of the cultures, is thermolabile, can be precipitated by ethyl alcohol and is sensitive to the digestive action of pepsin and pancreatin. It has the same characteristics as the hæmolysin in decomposed market milk, and the hæmolysin in the latter substance may reasonably be attributed to the development of this species. The possibility that other bacteria which produce hæmolytic substances may also be present in this milk must, of course, always be considered. The close correlation between the presence of the hæmolysins in milk and the presence of *Bacterium welchii* and the similarity in reactions of the hæmolysin in the heated market milk and of the hæmolysin in milk cultures of *Bacterium welchii* are both quite striking, however, and lend strong support to the view that this organism is the chief source of the hæmolysins in question. The hæmolysin of *Bacterium welchii* according to these observations belongs to the group of bacterial hæmolysins and is not to be attributed to any acids like butyric or lactic acid, which this species may produce in milk cultures. Both butyric and lactic acids are hæmolytic. When made up in a 1 per cent solution of the official acids they dissolve blood corpuscles rapidly, as can be seen from the following table:

TABLE X.

HÆMOLYTIC ACTION OF LACTIC AND BUTYRIC ACIDS FOR RABBIT'S CORPUSCLES.

Lactic acid, 1 % sol.		Rabbit corpuscles, 5 % suspension.		Hæmolysis.
.01 c. c.	+	1 c. c.	=	+ +
.0075 c. c.	+	1 c. c.	=	+ +
.005 c. c.	+	1 c. c.	=	+ +
.0025 c. c.	+	1 c. c.	=	+ +
.001 c. c.	+	1 c. c.	=	+ +
.00075 c. c.	+	1 c. c.	=	+
.0005 c. c.	+	1 c. c.	=	0
.0001 c. c.	+	1 c. c.	=	0

Control NaCl negative.
+ + = Complete hæmolysis.
+ = Partial hæmolysis.
0 = No hæmolysis.

Butyric acid, 1 % sol.		Rabbit corpuscles, 5 % suspension.		Hæmolysis.
.01 c. c.	+	1 c. c.	=	+ +
.0075 c. c.	+	1 c. c.	=	+ +
.005 c. c.	+	1 c. c.	=	+ +
.0025 c. c.	+	1 c. c.	=	+ +
.001 c. c.	+	1 c. c.	=	+
.00075 c. c.	+	1 c. c.	=	0
.0005 c. c.	+	1 c. c.	=	0
.0001 c. c.	+	1 c. c.	=	0

Control NaCl negative.
+ + = Complete hæmolysis.
+ = Partial hæmolysis.
0 = No hæmolysis.

Lactic acid thus hæmolyzes in a dilution of 1-1000 of a 1 per cent solution and butyric acid in a dilution of 1-400. The hæmolysed blood takes on a dirty-brown color characteristic of acid hæmolysis and never shows the clear solutions tinged with hæmoglobin produced by the true bacterial hæmolysins. Moreover, the hæmolysins of both lactic and butyric acids are thermostabile. If dilutions of 1-200 (.005 c. c. of a 1 per cent solution) be taken and tested for their power to resist heat it is found that their hæmolytic activity is not injured by exposure to high temperatures, even that of the boiling point. This is shown in the following table:

TABLE XI.

ACTION OF HEAT ON HÆMOLYTIC ACTIVITY OF LACTIC AND BUTYRIC ACID.

	Hæmolysis of 5 % rabbit's blood heated ½ hour to							
	Raw	50°C.	55°C.	60°C.	65°C.	70°C.	80°C.	90°C.	100°C.
Lactic Acid 1–200	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +
ButyricAcid 1–200	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +

The thermolabile hæmolysin in milk cultures of *Bacterium welchii*, therefore, cannot be attributed to either butyric or lactic acid. That these acids may play a rôle in the hæmolysis produced by the whey before neutralization is not denied, but we believe that this action on the blood corpuscles is an independent phenomenon. The hæmolysin in the neutralized cultures of *Bacterium welchii*, according to our present observations, is a true bacterial hæmolysin. Finally it is to be noted that the hæmolysins in decomposed market milk which we attribute to the presence of *Bacterium welchii* are also independent of both lactic and butyric acids, since like the hæmolysin in milk cultures of *Bacterium welchii* they are found in the milk after neutralization and are thermolabile.

SUMMARY AND CONCLUSIONS.

Market milk heated to 85° C. for 15-20 minutes and allowed to decompose by incubation at 22° C. or 37° C. for 24-48 hours contains an hæmolysin of moderate strength. This hæmolysin is independent of the acids in the milk, occurring in neutralized specimens, is thermolabile, being destroyed at temperatures between 55° C. and 60° C., is precipitable by ethyl alcohol and can be digested by pepsin and pancreatin. It is to be classed with the bacterial hæmolysins and is in all probability to be attributed to the presence of *Bacterium welchii* in the market milk. Pure milk cultures of *Bacterium welchii* contain a similar hæmolysin which is, however, usually slightly more powerful. This also is independent of the acids in the milk, is thermolabile, being destroyed at temperatures between 55° C. and 60° C., is precipitable by ethyl alcohol and can be digested by pepsin and pancreatin. On the basis of the work thus far completed we believe that this hæmolysin is a true bacterial hæmolysin. It is especially to be differentiated from the hæmolysin of both lactic acid and butyric acid, which are thermostabile. The rôle which these acids play in the hæmolysis seen in cultures of *Bacterium welchii* is, we believe, secondary to that of the true bacterial hæmolysin secreted by the organism.

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VENOUS CONGESTION IN ITS RELATION TO NECROSES OF THE LIVER.

By HORST OERTEL.

(From the Pathological Laboratories of the Royal Victoria Hospital and of McGill University, Montreal.)

It has become generally recognized that severe venous congestion in the liver may in a certain type of cases be associated with lobular necroses and that these may become extensive enough to lead to a very general disorganization of the liver substance, occasionally with deep jaundice, and clinically to coma and death. A discussion has arisen as to the cause of these necroses: A number of cases under my observation from 1903 to 1910 led me to the conclusion, stated first in a report of a case in the Archives of Internal Medicine (1910, vi, 293) and later in a general consideration of this lesion in the Berliner Klinische Wochenschrift (1912, Nr. 43), that these necroses were directly dependent upon the stasis and were not bacterial or toxic in origin.

Mallory, on the other hand, in an extensive study of this subject (Journal of Med. Research, 1911, xxiv, 455), regarded them essentially as bacterial and toxic in character.

This question was investigated experimentally by Bolton (Jour. Pathol. and Bact., 1914, xix, 258), who was able to produce exactly similar necroses by causing extreme congestion in the liver by partial and complete obliteration of the

vena cava in the monkey. Based on his results, Bolton decided that the cellular loss was directly due to passive congestion and not to bacterial infection.

The recent observations of Heinrichsdorff (Ziegler's Beiträge, 1914, lvii, 635), and especially of Lambert and Allison (Bull. Johns Hopkins Hospital, 1916, xxvii, 310), on human livers, also place the greater emphasis on the congestion itself and subordinate the importance of infections or of outside toxic factors. Similar views are expressed by MacCallum (Text-book of Pathology, 1916, p. 469). Although it seems, then, that the combined anatomical and experimental evidence favors the direct relation of cyanosis to the production of necroses, there is as yet no agreement or certainty as to the exact manner in which these necroses develop. MacCallum, Lambert and Allison look upon the necroses of the liver cells as the result of asphyxia, Hart as due to a lack of nutrient material owing to the formation of fibrin plugs in capillaries, Heinrichsdorff even regards them as due to an autointoxication caused by the higher CO_2 contents of the blood and the entrance of intestinal, harmful substances acting on depressed, poorly nourished, liver tissue.

My studies have led me to a different idea, which has been strengthened by recent observations. It is based directly on the anatomical evidence of the nature of these necroses, which, to me, appears highly significant in regard to the genesis of the lesion. For this reason I have in previous publications repeatedly emphasized that we are not dealing with ordinary necrotic changes, ushered in by marked parenchymatous degeneration, nuclear degeneration, protoplasmic coagulation and the formation of dead structureless masses, but with simple cell solution. The cells undergo œdematous swelling, the protoplasm becomes honey-combed and gradually dissolves; the nucleus persists until late, when it, too, disappears by simple karyolysis; the cell outlines remain and become even more distinct as the protoplasm dissolves; ultimately remains nothing of the cells, only a fine reticulum occupies the parts implicated. Fat occurs usually in large drops at the periphery of these necroses.[1] In other words these changes, from the start, are similar to œdematous imbibition and solution, and not at all in the nature of direct cell destruction that occurs from the effects of bacterial or toxic injury. This latter leads early, as is well known, to severe degenerative pictures in the protoplasm and nucleus of the cell, to obscurity of the cell outline and coagulation of dead protoplasmic masses. But these features are entirely absent in cyanotic necrosis.

Furthermore, it does not seem that interference with nutrition by asphyxia or lack of nutriment alone would explain these characteristic histological findings. I consider their relation to these cell changes, as will be explained later, an indirect one.

Now it might be doubted that even an extensive œdematous imbibition of the liver (admitting this to occur as the result of certain severe cases of cyanosis) would lead to such necroses. I have, however, been fortunate enough to be able to observe lately the liver in a case of fatal trinitrotoluene poisoning in a healthy, strong, muscular young man. (The case has been reported elsewhere by Dr. Odland, of this laboratory, Royal Victoria Hospital, Montreal, Scientific Reports, 1916, Series B. 1.) It appears that trinitrotoluene is essentially a vascular poison. It leads to massive œdema and hæmorrhages, but does not seem to display marked toxic affinity for the liver cells themselves. This liver presented histologically pictures very similar to cyanotic necroses, both in manner of formation and in the end product, viz., massive, intercellular œdema, followed by œdematous swelling, cytolysis and karyolysis of liver cells individually well outlined until late, without parenchymatous degeneration and coagulation necrosis. The end result was here also a hazy reticulum. The only difference from the changes in chronic cyanosis was a remarkable absence of fat in the surrounding liver cells, which are frequently very fatty in cyanotic necrosis.

Finally, a very similar, although more diffuse, type of cell degeneration and necrosis in the liver was observed by me several years ago in experimental uranium nephritis (A contribution to the knowledge of experimental nephritis, Lancet, May 23, 1914). Uranium, much like trinitrotoluene, produces in the liver as in the kidney a very marked œdema followed soon by tremendous swelling (hydrops) and solution of liver cells in a manner described above. As with trinitrotoluene, fatty changes are absent after the administration of large doses, whereas, on the other hand, œdema and cytolytic necrosis of the liver cells are most marked. I noted at the time that these changes are different from those caused by cantharidin and mercury, which display a pronounced toxic affinity for liver parenchyma as shown by definite parenchymatous degeneration and coagulation necrosis.

Based, then, on the characteristic type of necrosis in venous cyanosis and its similarity to others in which œdematous imbibition of liver cells also occurs, it seems to me reasonable to maintain, that, under certain conditions of severe cyanosis, increased transudation with stagnation occurs in the liver, as we know it to occur elsewhere. This leads primarily to passive swelling (hydrops) of liver cells, secondarily to their solution, possibly through the formation of a cytolytic ferment, and thus to characteristic liver necroses.

The extent and rapidity with which these form seem to depend, to some extent at least, upon the amount and stagnation of the transudate or œdema. Thus, they are more pronounced in severe advanced congestion. They assume, therefore, occasionally dimensions of such an extensive and often rapid disorganization of the liver as to lead to rapidly deepening jaundice and, clinically, to coma and death.

Finally, as to the cause of the œdema. Here, it seems to me, a number of factors contribute: First, impaired oxidation (asphyxia) of the cells and consequent accumulation of waste products lead to high osmotic pressure and increased

[1] The detailed description of the cell changes by Heinrichsdorff fully agrees with my own.

H ionization in the tissues;[2] secondly, increased transudation and lessened resorption of fluid result from diminished tissue tension and nutritional disturbances in blood-vessels and lymphatics. To these contribute further increased venous and lessened aortic pressure. Thirdly, gradual collapse of the lobule makes lymph circulation increasingly difficult and ultimately entirely impossible. This, together with hæmorrhages into the lost parts, hastens the terminal destruction of the lobule.

Although it appears that the accompanying jaundice is also a result of lobular disorganization, the exact manner in which this is produced must, like that of jaundice generally, be still determined by future research.

It may be asked why the liver is involved in these, often severe and general, cyanotic necroses in preference to other parenchymatous organs (the kidney for example). This may be due to its architectural arrangement and characteristic blood and lymph flow in which it differs from other organs; for the parenchyma cells, in forming pyramids around the central veins and columns, which stand in intimate contact on either side with blood and lymph capillaries, possibly even through intracellular canaliculi, are in closest connection with their circulation and not separated by any elastic stroma or basement membrane. To this must be added the, even normally, much retarded blood and lymph flow in the liver as compared with that in other glandular organs.

[2] See J. Loeb. Pflüger's Arch., 1898, 71, p. 457, on the relation of osmotic pressure to œdema.

OBSERVATIONS ON THE DEGENERATION OF LEUCOCYTES IN THE URINE AS A DIAGNOSTIC AID IN TUBERCULOSIS OF THE URINARY TRACT IN WOMEN.*

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In 1906 Colombino published the results of a cytological study of the urine in cases of pyuria, with reference to the diagnosis of tuberculosis of the genito-urinary tract. He concluded that in cases showing degenerated leucocytes and some red blood cells, a definite diagnosis of tuberculosis can be made.

These degenerated leucocytes are described as having variable forms; polyhedral, elongated and indented. In some cells the protoplasm seems to have been eaten out and considerably reduced about the nucleus. In other cells there are multiple vacuoles in the protoplasm and small balls of protoplasm at the periphery of the cells which seem detached from them. In many of these irregular cells the envelope seems to have burst. Free nuclei are also found.

Colombino attributed this degeneration to a specific toxic action of the tuberculous urine. He was unable to find any relation between the concentration, reaction or content in chlorides, phosphates, sulphates, urates and uric acid and the cytological picture.

Moscou, in 1907, reported a series of cases and the results of his studies on the cause of this degeneration. He concluded that it is independent of the reaction, concentration or content in urea and chlorides and that cryoscopic determinations shed no further light on the question, nor does the time of examination after voiding have any relation to the phenomenon.

Moscou added normal leucocytes to tuberculous urine and degenerated leucocytes to normal urine, but did not observe any change in the contour of the cells in either case. However, he found that if degenerated leucocytes are placed in isotonic salt solution, they become normal in form after from five to twenty minutes, and that this also occurs if a solution of picro-carmine is substituted for normal salt solution.

Goldberg states that he observed, in 1901, elongated and spindle-formed cells in tuberculous urine and that leucocytes in ameboid action also were seen.

Colombino found the cytological formula of tuberculous and non-tuberculous urines to be nearly always the same:

Polynuclear neutrophiles	90 – 95%
Mononuclears	10 – 5%

In one case of very long standing pyelitis with calculus, there were 67 per cent of mononuclears, and in another similar case 12 per cent of mononuclears.

His series of cases included 20 of genito-urinary tuberculosis, in all of which degenerated leucocytes and red blood cells were found, whereas in 13 cases of non-tuberculous pyuria, the leucocytes were well preserved, except in one case of renal calculus of long standing.

In Moscou's series of 50 cases, there were 22 of genito-urinary tuberculosis. In 18 of these degenerated leucocytes were present; in four there was no degeneration. He also observed leucocytic degeneration in two non-tuberculous urines.

Goldberg reported degeneration of leucocytes in 13 and no degeneration in four cases of urogenital tuberculosis; no degeneration in eight cases of kidney or bladder stone, and deformed cells in eight cases of gonorrhœa (acute and chronic) in four of which the majority of the leucocytes had become degenerated.

* Read before a meeting of The Johns Hopkins Hospital Medical Society, May 7, 1917.

TABLE I.—TUBERCULOUS CASES. OPERATED.

Gyn. No.	Age.	Operation.		Pathological.		Urine Examination.										
		Date.	Character.	No.	Diagnosis.	Date.	Voided.	Cath.	Time after collection.	R. B. C.	Ep.	Casts.	Bacilli.	W. B. C.	Reaction.	Culture.
21625	38	10/25/15	Nephrectomy, right.	21617	Tuberculosis of kidney.	10/25/15	.....	+	Immediate.	0	0	0	Non-motile rods. No tuberculosis, 4 smears.	Large amount of pus. Well preserved cells.	Acid.	
Med. 34925	21	.....	Nephrectomy.	....	Tuberculosis of kidney.	10/29/15	+	.....	Immediate.	+	+	0	Acid-fast bacilli.	Large amount of pus. Some degenerated cells. Majority well preserved.	Acid.	From both kidneys. No growth.
						11/4/15	.....	+	Immediate.	+	+	0	Tubercle bacilli.	About 30% show degeneration.	Acid.	
Miss F.	..	12/8/15	Nephrectomy, left.	....	Tuberculosis of kidney.	11/23/15	.....	+	Several hrs.	+	+	0	Tubercle bacilli.	Large amount of pus. Majority of cells degenerated.		
						12/3/15	.....	+	1 hour.	+	+	0	Tubercle bacilli.	Large amount of pus. Majority of cells degenerated.		
F. 47637	52	1/5/16	Nephrectomy and ureterectomy, left.	21798	Tuberculosis of kidney.	12/2/15	.....	+	Immediate.	+	+	0	Tubercle bacilli. Non-motile rods.	Large amount of pus. Majority of cells degenerated.	Acid.	B. coli, bladder and left kidney.
21859	..	.....	.....	....	.....	12/9/15	.....	+	Immediate.	+	....	0	Tubercle bacilli.	Same as above.		
21813	21	12/17/15	Nephrectomy, left.	21764	Tuberculosis of kidney.	12/15/15	.....	+	Immediate.	+	+	0	Tubercle bacilli.	Moderate amount of pus. 90% degenerated.	Neutral.	Staphylococcus albus bladder abscess. No growth.
19972	22	2/19/14	Nephrectomy, right.	19960	Tuberculosis of kidney, right. Now tuberculosis of left kidney.	2/18/6	.....	+	24 hours.	+	+	0	Tubercle bacilli.	Moderate amount of pus. 90% degenerated.		
						5/2/16	.....	+	24 hours.	+	+	0	Tubercle bacilli.	As above.		
						11/?/16	.....	+	48 hours.	++++	+	0	Tubercle bacilli.	As above.		
22040	24	3/22/16	Nephrectomy, left.	22002	Tuberculosis of kidney.	3/8/16	.....	+	Immediate.	++++	....	0	Tubercle bacilli.	Small amount of pus. Majority well preserved. About 20% degenerated.	Neutral.	Bladder and kidneys, right and left. No growth.
						3/18/16	.....	+	8 hours.	+	+	0	Tubercle bacilli.	As above.	Neutral.	
						3/20/16	+	.....	Immediate.	+++	0	0	.....	Majority well preserved. 20% irregular in outline.		
						4/18/16	.....	+	8 hours.	0	+	0	.....	A few W. B. C. well preserved.	Acid.	
22366	18	6/13/16	Nephrectomy, right.	22281	Tuberculosis of kidney and tuberculosis of bladder.	4/24/16	.....	+	Immediate.	+	+	0	Tubercle bacilli.	A few W. B. C. well preserved.	Acid.	No growth.
						4/18/16	.....	+ left kidney cath.	Immediate.	0	0	0	0	0	Acid.	
						4/18/16	.....	+ right kidney trans. vesicl.	Immediate.	0	+	0	Tubercle bacilli.	A few W. B. C. well preserved.	Acid.	
22709	33	11/27/17	Nephrectomy and ureterectomy, right.	22681	Tuberculosis of kidney and ureter.	11/14/16	.....	+	30 hours.	0	+	0	Tubercle bacilli.	Moderate amount pus. 40% degenerated.	Acid.	
						11/15/16	.....	+	5 hours.	+	+	0	Tubercle bacilli.	Moderate amount pus. 75% degenerated.	Acid.	No growth.
						11/27/16	.....	+	Immediate.	0	0	0	Tubercle bacilli.	Moderate amount pus. A few degenerated W. B. C.	Acid.	
Brooks	40	.....	Nephrectomy, right.	22803	Tuberculosis of kidney.	12/14/16	.....	+	Immediate.	+	0	0	Short motile rods.	Large amount pus. Majority degenerated.	Acid.	
						12/28/16	.....	+	Immediate.	0	+	0	Tubercle bacilli.	As above.		
Miss M.	18	2/23/17	Nephrectomy, right.	22858	Tuberculosis of kidney.	2/21/17	.....	+	Immediate.	+	+	0	Tubercle bacilli.	Large amount pus. About 5% degenerated.	Acid.	No growth.

TABLE II.—NON-TUBERCULOUS CASES. OPERATED.

Gyn. No.	Age.	Operation.		Pathological.		Urine Examination.									
		Date.	Character.	No.	Diagnosis.	Date.	Voided.	Cath.	Time after collection.	R. B. C.	Ep.	Casts.	Bacilli.	W. B. C.	Reaction.	Culture.
21509	30	11/6/15	Nephrotomy, right.	21602	Nephrolithiasis, right. Chronic interstitial nephritis.	11/6/15	.....	+	1½ hours.	0	+	0	Chains of cocci.	Large amount pus. Well preserved cells. A few slightly irregular in outline.	Acid.	Streptococcus.
22322	..	6/20/16	Nephrotomy, right.	22316	Nephrolithiasis, left.	6/20/16	Aspirated from kidney at operation.	.....	Immediate.	+	0	0	.....	No marked degeneration. Not as well preserved as usual.		
21700	55	1916	Nephrolithotomy, left.	....	Bilateral nephrolithiasis.	11/23/15	.....	+	Immediate.	++	+	0	Motile rods.	Large amount pus. Well preserved cells. Occasional slightly degenerated cells.	Acid.	
					Died after operation.	11/23/15	.....	+ right kidney.	Immediate.	+++	+	0	Motile rods.	Large amount pus. Well preserved cells. A few degenerated cells.	....	B. paratyphosus.
					Streptococcus cellulitis around wound.	11/23/15	.....	+ left kidney.	Immediate.	+	+	0	Motile rods.	Moderate amount pus. Well preserved cells. Occasional slightly degenerated cells.	....	B. paratyphosus.
21716	38	12/2/15	Repair of post-operative vesico-vaginal fistula.	....	....	11/29/15	+	+	Several hrs.	0	+	0	0	A few W. B. C. Well preserved.	Acid.	
						12/5/15	.....	+	6 hours.	0	+	..	.....	Numbers of W. B. C. Majority well preserved. A few slightly irregular in outline.	Acid.	
21087	61	1/27/16	Partial resection of bladder.	21855	Carcinoma of bladder.	1/25/16	.....	+	Immediate.	+++	+	0	Bacilli.	Small amount pus. Well preserved.		
						3/19/16	+	+	30 hours.	++++	0	0	.....	Large amount pus. Well preserved.	Acid.	
22029 Col'd.	37	2/16/16	Nephrectomy, left.	22029	Pyonephrosis, nephrolithiasis.	2/14/16	.....	+	Immediate.	0	+	0	Non-motile rods.	Large amount pus. Well preserved.	Acid.	B. typhosus and Streptococcus.
21900	9	3/1/16	Nephrectomy, right.	21935	Pyonephrosis.	2/24/16	.....	+	Immediate.	+	+	0	Non-motile rods.	Large amount pus. Well preserved. Occasional slightly irregular cells.	Acid.	B. coli.
								Right kidney.	Immediate.	+	+	0	Non-motile rods.	Same as above.	Acid.	
22578	34	10/20/16	Nephrolithotomy, right.	22587	Nephrolithiasis.	10/14/16	.....	+	Immediate.	0	+	0	0	Small amount pus. Well preserved.	Acid.	Staphylococcus albus.
						10/19/16	.....	+	Immediate.	+	+	0	Cocci.	Same as above.		
22497	55	10/23/16	Autopsy. No operation.	4902	Pyonephrosis, left.	10/20/16	.....	+	Immediate.	0	0	0	Bacilli.	Well preserved.	Acid.	No growth.
22683	38	12/6/16	Nephrotomy, right.	22697	Nephrolithiasis.	12/6/16	.....	+	1 hour.	+	+	0	0	Small amount pus. Well preserved.	Acid.	
22819	46	1/27/17	Nephrectomy, left.	22802	Nephrolithiasis, pyonephrosis.	1/27/17	.....	+	Immediate.	0	0	0	Non-motile rods.	Large amount pus. Some broken cells.	Neut.	Staphylococcus albus.
F 64156	57	12/20/16	Nephrectomy, right.	22724	Hypernephroma.	.....	.....	+	Immediate.	+	+	0	0	Well preserved. Small number W. B. C. in centrifugalized specimen.		
Mrs. F	30	6/18/16	Nephrolithotomy.	....	Nephrolithiasis.	6/15/16	.....	+	6 hours.	0	+	0	Urine not kept sterile.	Large amount pus. Well preserved.		
21855	50	1/26/16	Nephrolithotomy, bilateral.	21850	Nephrolithiasis, bilateral.	1/26/16	.....	+	Immediate.	0	0	0	0	Large amount pus. Majority well preserved.		
								Right kidney.	Immediate.	0	0	0	0	Same as above.		
								Left kidney.	Immediate.	+	0	0	0	Very few W. B. C. Many irregular. No marked degenerative forms in any specimen.		
22109	49	5/2/16	Nephrectomy, right.	22145	Hydronephrosis, chronic nephritis. Double kidney pelvis.	5/2/16	.....	+	1 hour.	0	0	0	Bacilli.	Moderate amount pus. Majority slightly irregular in outline and no marked degeneration.	....	No growth, right kidney.
22164 Col'd.	38	6/3/16	Pelvic puncture.	Autopsy 4718 6/9/16	Pelvic abscess, rupture into peritoneal cavity and bladder. General peritonitis.	6/5/16	.....	+	Immediate.	0	0	0	0	Large amount pus. Well preserved.	Acid.	No growth from bladder.
22137	37	12/22/15	Cystostomy.	....	Chronic ulcerative cystitis.	12/12/15	+	.....	8 hours.	+	++	0	.....	Large amount pus. Majority well preserved. Occasional degenerated W. B. C.	Acid.	B. coli.
						12/14/15	.....	+	Immediate.	+++	+	0	Non-motile rods.	Large amount pus. Considerable number show slightly irregular outline.		

TABLE II. OPERATED—CONTINUED.

Gyn. No.	Age.	Operation. Date.	Operation. Character.	Pathological. No.	Pathological. Diagnosis.	Urine Examination. Date.	Voided.	Cath.	Time after collection.	R. B. C.	Ep.	Casts.	Bacilli.	W. B. C.	Reaction.	Culture.
22137	37	.....	.....	....	.....	12/20/15	.....	+	5 hours.	+++	+	0	Non-motile rods.	Majority well preserved. A few slightly irregular W. B. C.		
						1/25/16	.....	+	.....	++++	+	0	Non-motile rods.	Well preserved.	....	B. coli.
								+	Immediate.	+++	0	0	Non-motile rods.	Some slightly irregular cells.		
								Left kidney.	Immediate.	++++	+	0	0	Occasional W. B. C. Well preserved.	....	Culture before discharge.
							+	.....	8 hours.	++	+	0	.....	Majority well preserved. Some irregular cells.	....	No growth.

TABLE III. NON-TUBERCULOUS CASES. NOT OPERATED.

Gyn. No.	Age	Diagnosis.	Urine Examination. Date.	Voided.	Cath.	Time after collection.	R. B. C.	Ep.	Casts.	Bacilli.	W. B. C.	Reaction.	Culture.	Remarks.
21651	19	Gonorrheal cystitis, acute.	11/4/15	.....	+	Immediate.	0	+	0	Intracellular gram-negative diplococci.	+ Well preserved.	.....	No growth.	Well.
F 64014	34	Gonorrheal trigonitis and urethritis, acute.	10/14/16	.....	+	Immediate.	+	+	0	do.	+ do.	.....	No growth.	Well.
			10/24/6	.....	+	Immediate.	+	+	0	do.	+ do.			
F 60393	25	Gonorrheal cystitis acute.	8/10/16	.....	+	Immediate.	++	+	0	do.	++ do.	.....	No growth.	Well.
21898	23	Gonorrheal cystitis, acute.	1/13/16	.....	+	Immediate.	++	+	.....	do. No T. B.	+ do.	.....	No growth.	Well.
21832	40	Chronic cystitis.	1/25/16	.....	+	Immediate.	0	+	0	Non-motile rods.	++ do.	.....	B. coli.	Well.
F 1111	60	Acute cystitis.	6/29/16	.....	+	Immediate.	0	+	0	Bacilli.	++ do.	.....	.....	Well.
21645	49	Post-operative cystitis.	11/6/15	.....	+	4 hours.	0	+	0	.....	+ do.	.....	.....	Well.
			11/25/15	.....	+	Immediate.	+	+	0	.....	+ do.	Acid.		
			12/5/15	.....	+	4 hours.	0	+	0	.....	++ do.			
22080	59	Cystitis.	4/13/16	.....	+	½ hour.	0	+	0	Non-motile rods.	++ do.	.....	No growth.	Well.
21696	60	Chronic cystitis.	11/20/5	.....	+	2 hours.	+	+	0	do.	+++ do.	Alk.	B. coli and Staphylococcus albus.	Well.
Med. 36051	50	Cystitis.	3/13/16	.....	+	Immediate.	+	+	0	do.	+ do.	....		
			... ..	.....	Kidneys	.....	.....	.....	.....	.....	0 do.	.....	No growth.	Well.
22594	35	Bladder ulcer, cystitis.	10/5/16	.....	+	3 hours.	++	0	0	Non-motile rods. No T. B.	++ do.	.....	No growth.	Well.
21659	22	Bladder ulcer, cystitis, Ureter stricture.	11/30/16	.....	+	2 hours.	++	+	0	No T. B. 7 stains.	+ do.	Acid.	No growth.	Well.
21779 F 45822	28	Bladder ulcer, cystitis.	12/23/15	.....	+	Immediate.	+	+	0	.....	++ do.	.....	.....	Well.
Surg. 40401	30	Catheter cystitis and pyelitis (spinal cord tumor.)	9/18/16	.....	+	Immediate.	0	0	0	Non-motile rods.	+++ do.	.....	B. coli.	
			7/18/16	.....	+	Immediate.	0	0	0	do.	+++ do.			
F 61602	50	Chronic ulcerative cystitis. Hydronephrosis, infection right.	11/7/16	.....	+	Immediate.	+	0	0	do.	++ do.	.....	B coli.	Greatly improved
21945	11	Bilateral pyelitis, strictures of ureters.	2/25/16	.....	+	3 hours.	0	0	0	Bacilli. No T. B.	++ do.	Acid.	B. coli.	Well.
21908	32	Trigonitis.	2/14/16	.....	+	Immediate.	+++	0	0	No T. B. Examined 3 times.	+ do.	Acid.	B. coli.	Well.
		Urethritis.	.....	.....	Kidneys	.....	.....	.....	.....	.....				
21763	56	Trigonitis. Urethritis.	12/14/15	.....	+	Immediate.	0	0	0	.....	+ do.	.....	B. coli.	Well.
Mrs. K.	..	Acute pyelitis.	10/5/16	.....	+	Immediate.	0	0	.....	.....	++ Marked degeneration.	.....	.....	Well.

Two cases of renal tuberculosis showing degeneration of leucocytes were reported by Micheli.

Lequeux (quoted by Micheli) found degeneration present in both tuberculous and non-tuberculous urines.

Kelly and Burnam were unable to substantiate the observations of Colombino.

Colombino demonstrated the tubercle bacillus in only six of his 20 tuberculous cases. Micheli did not find the tubercle bacillus in either of his cases. Moscou says the tubercle bacillus was found rarely in his series, but does not mention the exact percentage.

In our 11 cases of renal tuberculosis, the tubercle bacillus was demonstrated in 10. Unfortunately the other case did not show any leucocytic degeneration, nor were red blood cells seen in one examination.

Acid-fast bacilli have not been found in any case of non-tuberculous pyuria, although numerous smears have been examined carefully.

Our notes include 72 cases of pyuria, in 27 of which the possibility of tuberculosis could not be positively eliminated, and these cases have not been tabulated. The majority of these patients were not under observation long enough to be thoroughly studied.

The tables include 11 cases of renal tuberculosis, for which nephrectomy was performed, 15 cases of non-tuberculous pyuria in which the possibility of tuberculosis was definitely eliminated by operation or autopsy, and 20 cases in which there was no operation but the clinical picture and results of treatment rule out tuberculosis.

TABLE IV.

Type of case.	Operation + or 0.	Number of cases.	Degeneration +	0
Tuberculosis of kidney	+	11	Marked in 6. Moderate in 1.	4
Nephrolithiasis	+	8	Variable but never marked, 2.	6
Pyonephrosis without stone	+	2	0	2
Hydronephrosis	+	1	Majority WBC. sl. irreg.	—
Hypernephroma	+	1	0	1
Carcinoma of bladder	+	1	0	1
Pelvic abscess with rupture into bladder	Autopsy	1	0	1
Cystitis, gonorrheal	0	4	0	4
Cystitis, general (B. coli)	0	6	0	6
Cystitis, general ulcerative	+	1	Moderate in some specimens, others well preserved.	—
Cystitis, general with pyelitis	0	1	0	1
Cystitis, general ulcerative, with infected hydronephrosis	0	1	0	1
Pyelitis, acute	0	1	Marked.	—
Pyelitis and ureter stricture, bilateral	0	1	0	1
Pyelitis and ureter stricture, unilateral	0	1	0	1
Bladder ulcer	0	3	0	3
Trigonitis and urethritis	0	2	0	2

The voided urine from five patients contained well-preserved leucocytes, whereas in the catheterized specimens there were no leucocytes.

TECHNIQUE.

Colombino studied both fresh preparations from the centrifugalized sediment and stained smears, but concluded that the fresh unstained preparations were preferable, as in stained smears irregularities of the cells can be produced artificially. The fresh preparations consist of a drop of centrifugalized sediment on a slide covered with a cover-glass and can be examined with the high-dry lens or oil-immersion lens. Goldberg examined fresh preparations without a cover-glass in order to eliminate a possible source of trauma to the leucocytes.

We have examined most of our specimens with and without cover-glasses and in a blood-counting chamber, but have not observed any cellular irregularities caused by the cover-glass.

The specimens of urine examined were usually obtained by catheterization of the bladder or ureters, but numerous voided specimens have also been examined. In women it is necessary to obtain catheterized urine for a diagnosis of pyuria. Specimens have been examined immediately and several hours after collection. There is no evidence that the leucocytes degenerate after standing for from 12 to 24 hours, although we believe the specimen should be examined soon after collection. Some of the specimens have been centrifugalized and others have not.

The culture work has been done in the Medical Bacteriological Laboratory by Doctors Clark and Sydenstricker.

CONCLUSIONS.

Degenerated leucocytes in the urine are not pathognomonic of tuberculosis of the urinary tract, but a marked degeneration is strongly suggestive of this disease.

The absence of degeneration of leucocytes does not eliminate tuberculosis.

The cytological study of the urine cannot replace the demonstration of tubercle bacilli or animal inoculation as a means of diagnosis; at best it offers presumptive evidence.

I wish to thank Dr. H. A. Kelly for permission to publish these observations, and Doctors Hunner, Leonard, Holmes and Richardson for their assistance and suggestions.

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THE ETHICS OF THE PRACTICE OF MEDICINE FROM THE JEWISH POINT OF VIEW.[1]

By Dr. Harry Friedenwald.

No people have laid greater emphasis upon the sacredness of life than have the Jews. The human being reflected the holiness of God, for "in the image of God made He man" (Gen. I, 27). But life itself, even the life of the lower animals, was held dear, for "the righteous man regardeth the life of his beast" (Prov. XII, 10). To care for one's health was regarded as a religious duty.

The people who looked upon life as sacred were naturally solicitous in their care of the sick. One of the highest duties was to visit the sick, and in the Talmud we read that this obligation extended equally to visiting the Gentile and the Jew. (Talmud, Gittin 61a.) This was in conformity with the verse "Thou shalt not abhor an Edomite, for he is thy brother; thou shalt not abhor an Egyptian, because thou wast a stranger in his land" (Deut. XXIII, 8). The tolerant spirit of the Jew was shown in his readiness to help the Gentile in distress.

Throughout Hebrew literature we find the most humane references to the sick. Thus in the Sefer Hasidim of R. Judah of Ratisbon (12-13th cent.) we read:

If a rich man and a poor man be sick and thou seest all the world going to see the rich man, go thou to the poor one, even though he be ignorant and unlectured . . . . Make no sign of visible disgust when thou meetest people afflicted with loathsome visible disease; for they are God's creatures, remember, and healthy as well as sick are all alike dependent upon him.[2]

The duty to treat the injured is expressed in Exodus (XXI, 18, 19): "And if men contend, and one smite the other with a stone or with his fist, and he die not, but keep his bed; if he rise again, and walk abroad upon his staff, then shall he that smote him be quit; only he shall pay for the loss of his time, and shall cause him to be thoroughly healed."[3]

This is not the occasion to discuss the theological dispute as to the propriety of any human interference in disease, looked upon as a visitation of God. Though the dispute was waged for a long time in Judaism and in Christianity, the practice of medicine won its proper position among the Jews at an early date. We are not surprised to learn that the Jews made great demands of the physician, that the ethical standards they set up for him were very high. Could less have been expected of those who followed the profession of Him who said: "I am the Lord that healeth thee" (Exodus, XV, 26).

It was regarded as proper that the physician should receive recompense for his service. Of course this was not to act as a hardship to the poor. We read that Abba (a leech and therefore belonging to a class that did not enjoy the same esteem as did the physician) had in his office a money-box into which those who received treatment would place what they desired to give. But no one could tell how much or how little each one paid. When a learned man came he would accept no payment, and if the patient was poor he would help him with a gift and refuse to accept any fee. (Talmud Taan. 21b.)

The physician was expected to treat his patients in a sympathetic and humane manner. This is beautifully shown in a passage in the Midrash, the ancient homiletical exegesis of the Thora:

Even when the physician sees that death is approaching, he still says to the patient "Eat this and abstain from that, drink this and not that," but he does not say "Your end is near," and it rebukes the prophet Isaiah in the name of King Hezekiah for telling him bluntly "Set thy house in order for thou shalt die and not live" (II Kings XX, 1).[4]

In the great code, the Shulhan Aruch, which Rabbi Joseph Caro[5] wrote in the third quarter of the 16th century and which embodies rabbinic laws, we find an important chapter dealing with the rules governing the practice of the physician.[6]

Text of Rabbi Joseph Caro.

1. The Thora permits the physician to treat disease. It is a meritorious act to do so, under the general principle of saving a life in danger. One who refrains from doing so, sheds blood [*i. e.*, is guilty of sacrificing life]. Even if there is another who can treat the sick man, the physician dare not refuse his services, because it is not through the aid of every man that the patient has equal chances to be cured. Yet should no man occupy himself with medicine, unless he is well trained and there is no one better fitted than he in the place; otherwise, he is shedding blood. If one treats a patient without the approval of the court [official license] he is in duty bound to pay damages, even though he is an expert. And if he treats a patient with the approval of the court and errs and injures the patient, he is not responsible to the human court but he is not absolved from his obligations to the higher, the heavenly court. If he kills the patient through negligence and he becomes aware that he is guilty of unintentional murder, he goes into exile [as "the manslayer that kills any

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[2] See Zunz: Jewish Moralists *in* "Hebrew Characteristics." American Jewish Publication Society, New York, 1875, p. 22.

[3] A curious version is found in the Vulgate and other translations: "That he make restitution for his work and for his expenses upon the physicians." (See Douay Version.)

[4] This subject is taken up in detail by Preuss, Virchow's Arch., CXXXVIII, 280.

[5] R. Joseph Caro was born in Portugal in 1488 and died in Safed, Palestine, in 1575.

[6] Shulhan Aruch Yorah Deah, 336.

person through error." See Numbers, XXXV, 9-34: Deut., XIX, 1-13.][1]

2. A physician is prohibited from taking a fee for his expert knowledge or for instruction, but only for his pains and for the time he spends.

3. If one has drugs and his sick neighbor wishes to buy them, he is prohibited from raising the price higher than is proper. Furthermore, if they agreed upon a high price because of the exigencies of the moment (for he was the only one who had these drugs) he may claim only their proper value. However, if the patient agreed to pay a large fee to a physician (for his services), he must pay it, because the physician sold his expert advice. The patient has no further redress.

Annotation by Rabbi Moses Isserles to Rabbi Joseph Caro:[2] It is true, it is a duty incumbent (upon the physician) to treat (the patient). For it is commanded that everyone come to the help of one whose life is in danger. If, however, the performance of this duty falls to one who refuses to act without remuneration, the court cannot deprive him of his fee. Neither can it release those who obligated themselves from fulfilling this obligation. (This is based upon a quotation from Rabbi Jacob ben Asher on the authority of Rabbi Moses Nachmanidis.)[3]

In the writings of Jewish physicians of early and later mediæval times there are a number of references to medical ethics; some of these deserve consideration. An essay has recently appeared by Professor Ludwig Venetianer on Asaf Judaeus, whom he describes as the oldest medical writer in Hebrew (Budapest, 1915). He shows that Asaf Judaeus wrote various works on cosmography and medicine, and he gives evidence to prove that Asaf lived at the latest in the 7th century and in Mesopotamia. The words of admonition which Asaf and his colleague John spoke to their pupils and the oath which they required of them are of great interest to us:

Beware of causing death to anyone by administering the juices of poisonous roots. Do not administer to an adulterous wife an abortifacient drug. Let not the beauty of woman arouse in thee the passion of adultery. Divulge not any secret entrusted to thee and do no act of injury or of harm for any price. Do not close thy heart to mercy toward the poor and the needy. Say not of the good that it is evil, nor of the evil that it is good. Walk not in the path of sorcerers who raise enmity in marital couples through incantation, magic and witchcraft. Do not covet any possession as a reward for having aided in an act of infamy. In thy treatment do not apply the arts of the idolater, and place no trust in idols, for they are naught and are of no avail. On the contrary, ye must despise their servants; dead spirits are their idols without ability to help their lifeless images; how much can they avail the living human beings? Put thy trust in the Eternal, the God of Truth; He kills and He likewise brings to life; He punishes and He heals the wound; He gives to man understanding to be of help; He punishes in righteousness and justice, but He restores in love and in mercy; He makes plants of healing to grow up and he implants into the perfect heart the ability to heal, in order to make known His great grace and his wondrous works before great multitudes, so that all living may understand that He is the Creator and beside Him there is none who can help. The nations place their trust in idols who cannot help them in the hour of need, nor save them in their distress; thus their hope and their longings lead unto death. It is proper, therefore, that ye separate yourselves from them, that ye keep yourselves far removed from their idols

[1] The responsibility of the physician is formulated in the Tosefta, an ancient collection of detailed statements of the traditional law. Tosefta (ed. Zuckermandel), Gittin, IV, 6. A professional doctor, authorized by Beth Din, who has caused harm to his patient is free if the error was unconscious but guilty if it was knowingly committed, for the sake of the social order.

Ibid., Baba Kama, VI, 17: A professional doctor authorized by Beth Din, who has harmed his patient is free before a human tribunal, and his judgment is referred to Heaven.

Ibid., X, 11: A professional doctor authorized by Beth Din who has caused harm to his patient is free; if he has wounded him more than was necessary, he is guilty.

Ibid., Makkot, II, 5: A professional doctor authorized by Beth Din who has caused the death of a patient is exiled (to the cities of refuge). This holds true only if the doctor did just what was required: but if he has exceeded the limit and thereby caused death, he is not exiled because he is guilty wittingly. Nevertheless, he does not incur the penalty of death.

That the passages are not altogether consistent is quite apparent and Duran summarizes his exposition of these laws as follows: "If a physician authorized by Beth Din to practice caused harm to his patient, which other physicians discovered to be due to his error, then he is legally guilty of assault whether the error was committed consciously or unconsciously. If he caused death, he has the status of a murderer. But if he made no error in the nature of the treatment and was unsuccessful in carrying it out, then for the sake of the social order (*i. e.*, that the doctors should not give up their profession) he is acquitted by the human tribunal and his judgment is referred to Heaven; while, if he caused death, he is exiled. If, however, he exceeded the necessary measures, then he is guilty of assault or murder and must pay damages in the one case, and the penalty of death in the other event, if he was forewarned, or left to the vengeance of the 'redeemer,' if he was not warned." Duran, who was himself a physician, (Respona, Part II, No. 52), ends this paragraph with the pious wish: "And may God grant our portion to be among those who are successful in their profession and may He save us from errors, Amen."

It is here that Duran proceeds to draw the contrast between medical doctors and surgeons, thus: "It appears that by 'Rophe umman' is meant one who heals wounds with the work of his hands. If he commits an error consciously or unconsciously, he inflicts a bruise; if he uses a metallic instrument he causes death . . . . but one who cures the sick with medicines, laxatives, drugs, baths, and resting is not called 'Rophe umman' but 'Rophe' and is not included in the former category. He cannot be sued for damages as he did not wound his patient. If such a physician commits an error and causes death or increases the suffering of his patient, he is free even before the judgment of Heaven, if his intentions were to cure and not to harm the patient. For he can judge but what his eyes see. But he must not rely upon his own experiments and reject the opinion of greater experts. If a doctor conducts himself rightly and properly, his Heavenly reward will be great, because his profession is a dangerous one and he must have exercised great caution." (This account of the Tosefta has been given me by Dr. A. A. Neuman.)

[2] Rabbi Moses Isserles lived in Crakow from 1520-1572. His annotations are regarded as essential and as binding, especially by the Askenasic Jews.

[3] The translation from the Shulhan Aruch has been prepared by Dr. Rabinowitz.

and that ye call upon the name of the Eternal, the living God, the God of the spirits of all flesh, in whose hand lies the power over the souls of all living and the spirits of all mankind, to kill or to bring to life; no one can escape from his might. Keep Him in mind at all times, seek Him in truth, rectitude, and perfection; then will all the works of your hands succeed. He will help you to be of aid to others and ye will be praised highly by all mankind; the people will forsake their idols for the service of the Eternal, for they will recognize that they had placed their trust in nought, that they had wearied themselves in vain in the service of gods which cannot be of help. Therefore be ye strong and not indolent, for great reward awaits your work. God will be with you, if ye are with him. If ye keep the covenant of your oath and if ye follow our instructions, then ye will be honored as saints in the eyes of all mankind who will say: "Happy the nation whose God is the Lord; the people whom he has chosen for his own inheritance." (Ps., XXXIII, 12).

Then the pupils answered and said:

Everything concerning which ye have admonished us, and everything which ye have commanded us, we shall heed, for it is the law of the Thora and it is our duty to obey it with pure heart, with whole soul and with all our strength and not to depart from it either to the right or to the left.

Thereupon they blessed the pupils in the name Almighty, the Creator of heaven and earth, and they continued to speak words of caution to their pupils and they said:

See the Eternal, His Holiness and His Thora are the witnesses that ye fear Him and that ye will not swerve from His laws but that ye will follow his commandments and that ye will not depart from the straight path, in order to gain profit from helping him who is lying in wait for the innocent soul, or from him who mixes poison to kill. Do not make known to anyone which plants are poisonous, nor give them to anyone. Allow no one to persuade you in any manner to produce disease in any one. Take heed lest ye cause any bodily deformity whatsoever and be not too much in haste to apply the knife. Do not apply cupping immediately but only when ye have considered and examined carefully two and three times, then only shall ye apply this remedy. Beware lest the spirit of pride come upon you and lest ye bear revengeful hate against any sick one. In your speech be upright and truthful, then will ye find grace in the eyes of God and among men will ye be regarded as honest, trustworthy and upright physicians.

One of the most remarkable statements bearing upon ethics of medical practice from the Jewish point of view is to be found in the "Aphorisms" or "Introduction into Medicine" of Isaac Judaeus, consisting of 50 articles.[10] Isaac Judaeus (Abn Jacob Ishak ben Soleiman El-Israeli) is a name well known in medicine. He was born in Egypt about 830, lived in Mauretania and Cyrenaica (Northern Africa) and died about 932. The following is a translation of a number of the aphorisms:

(2) As the science of medicine is so extensive and the life of man too short to attain the whole, physicians of experience must be separated from the foolish, they must "purify themselves, make themselves white and be refined" (Daniel XII, 10), for by their constant study of literature and ceaseless investigation they distinguish themselves from the rest of mankind.

(3) The rapidity or slowness or hesitation in the work of an artisan depends upon the importance or unimportance or indifference of the object upon which he is working. He, who is busied in drilling openings in pearls must be very careful not to destroy the beauty of his work through haste. But it is different with him who is collecting the filth of the street. It is fitting that he who is engaged in the cure of human bodies (which are the most precious of all of the creations of this nether world) consider and examine carefully the diseases that may occur, and give his directions after mature deliberation and consideration so that he make no irreparable error. Therefore the sage (Mesue) says: "If you find a physician who is ready as soon as asked to give information about every disease and particularly to praise his own methods of treatment, you may regard him as a knave." The prince of physicians (Ibn Zoar) says: "I have never given a person a purge without having been anxious in my mind and having spent sleepless nights before and after."

(4) Just as the physician, according to what has just been said, should not be over hasty in acting, so he dare not be negligent or dilatory, for in the case of most diseases there is no time to be lost. He should, on the contrary, hold to the mean between these extremes and be neither too hasty and precipitate nor too tardy and negligent; in acute diseases he must think and act quickly because they are pressing.

(11) The physician does not bring about the cure, but he prepares and smoothes the way for nature; nature is the actual healer.

(15) The need of the physician is twofold, preserving health and curing disease; and the demand for the former is greater than for the latter; for it is better for man that he avoid becoming ill than that he become ill and be cured.

(17) The physician who promises to cure disease with certainty takes a serious responsibility upon himself. . . . .

(21) If it is possible to bring about a cure by means of foods or healthful nourishment, then do not administer drugs because these, and especially the purging ones, are contrary to nature and are her enemies.

(23) Endeavor in thy treatment always to use the simple drugs, because it is easier for thee to acquire the knowledge of their action than that of the complicated ones.

(25) Never rely in treatment upon wonderworking cures, for these depend mostly upon ignorance and superstition.

(27) It is fitting to the profession of a physician that he should be moderate in eating—that he should not become a debaucher nor a glutton. It is a shame and a reproach, if he suffer from tedious illness, for then the people will say: "How should he who cannot cure himself, cure others?"

(28) Seal thy mouth to prophetic and self-evident expressions. What thou sayest should generally be stated as conditional.

(29) Suffer not thy mouth to condemn when something happens to a physician, for everyone has his evil day. Let thy deeds praise thee, and seek not thine honor in another's shame.

[10] Published with German translation by David Kaufmann, in 1885.

(30) Make it thy special concern to visit and treat poor and needy patients, for in no way canst thou find more meritorious service.

(31) Try to ease the mind of the patient, encourage him to look forward to being cured, even if thou are not thyself convinced of it, for this will greatly strengthen his nature.

(38) When the patient does not follow thine injunctions or his servants and people do not promptly obey thine instructions or show thee the proper respect, it were better to give up the treatment.

(39) Fix the fee of thy patient when his disease is in its ascendency and most severe, for as soon as he is cured he will forget what service thou hast rendered.

(40) The more thou demandest for thy service, the higher thou fixest the fee for thy treatment, the greater will they appear in the eyes of the people. Thine art will be looked upon as insignificant by those whom thou treatest for nothing.

(42) Do not visit thy patient too often and do not remain with him too long, unless the treatment of the disease demands it, for it is seeing the doctor anew that gives joy to the patient.

(43) Too large a practice confuses the judgment of the physician and causes him to give mistaken directions.

(46) Be concerned in the treatment of princes and the wealthy, for they will be liberal to thee with their means, will always praise thee and will be devoted to thee after their cure, while the common nobodies, when they are cured, will even hate thee when they think of the fee which thou hast taken from them (Prov. XXIII, 7).

(50) Excessive activity and effort diminishes the power of the physician and weakens his spirit, for he must constantly think and be concerned about each patient, hopeful for his recovery, and pray for him as though he were "one of his kin, that is near to him" (Lev. XXI, 2).

An interesting glimpse into the rules of medical conduct is given in the will of Judah ibn Tibbon, a famous Jewish scholar, translator and physician, who lived in Granada, Spain (1120-1190). The following is taken from the ethical will of Judah ibn Tibbon to his son:[11]

My son, let thy countenance shine upon the sons of man; visit their sick, and let thy tongue be a cure to them; and if thou receivest payment from the rich, attend gratuitously upon the poor; and the Lord will requite thee, and give thee thy reward. Thus shalt thou find favour, grace, and good understanding, in the sight of God and man; thou wilt be honoured by high and low among Israel and the nations; thy good name will go forth far and near; thou wilt rejoice thy friends, and make thine enemies and adversaries jealous. Thou knowest already what is said in the Mibchar Hapeninim: "He who is desirous of having revenge on his enemies, should strive to improve himself to perfection." . . . . My son, accustom thyself to examine the drugs and medicinal vegetables one day every week; and do not apply an article which thou dost not thoroughly understand . . . . Why shouldest thou not be ashamed of thyself, and of the people, who all know that it is owing to thine intemperate diet that thou art sick every year? Indeed, there is no greater shame and disgrace than that of a physician to be ill from intemperance, one who is to mend others and cannot mend himself.

[11] Published by Edelman, London, 1852, pp. 8 and 14.

From the Responsa of Ibn Adret in the 13th century we cull the following: Asked whether a Jewish doctor may render obstetric service to a Christian woman, he replied that it was his duty to give his service to all who asked for it, to Jews and Christians alike and that his teacher, Nachmanides, had often treated Christian women.

I shall close this account with a reference to Amatus Lusitanus, eminent as a physician and medical writer, the vicissitudes of whose life portray those of his people during the middle ages. Born in 1511 in Portugal, he was reared as a Marrano (secret Jew). He was driven from his home by the inquisition and spent some time in Antwerp, Ferrara (where he taught medicine) and Rome and then settled in Ancona about 1549 where he resumed his family name and again professed Judaism. He acquired an extensive practice and was even called upon to treat Pope Julius III. But his persecution did not end and he was forced to migrate, finally reaching Salonica (about 1558) where he died of the plague in 1568.

He published works on medicine in the form of case histories, 100 in a volume, entitled "Centuries." The last of these, the seventh, written 1559, was published under the title "Curationum medicinalium centuries VII." It closes with the following oath or declaration, which gives expression to his views on the duties and ideals of the physician.

The Oath of Amatus.

I swear by the Eternal God and by His ten most holy commandments which were given on Mount Sinai, through Moses as lawgiver, after the people had been freed from their bondage in Egypt, that I have never, at any time, done anything in these my treatments save what inviolate faith handed down to posterity; that I have never feigned anything, added anything or changed anything for the sake of gain: that I have always striven after this one thing, namely, that benefit might spread forth to mankind; that I have praised no one, and censured no one merely to indulge in private passions, unless zeal for truth demanded this. If I lie, may I incur the eternal wrath of God and His angel Raphael, and may nothing in the medical art succeed for me according to my desires. Concerning the remuneration, furthermore, which is commonly given to physicians, I have not been anxious for this, but I have treated many, not only zealously, but even without pay: and have unselfishly and unswervingly refused several rewards offered by many people; and have rather sought that the sick might, by my care and diligence, recover their lost health than that I might become richer by their liberality: all men have been considered equal by me of whatever religion they were, whether Hebrews, Christians, or the followers of the Moslem faith. As concerns loftiness of station, that has never been a matter of concern to me, and I have accorded the same care to the poor as to those born in exalted rank; I have never brought about sickness; in diagnosis I have always said what I thought to be true; I have unduly favored no venders of drugs, except perhaps those whom I

knew to surpass the others by reason of their skill in their art or because of their natural qualities of mind; in prescribing drugs I have exercised moderation in proportion as the powers of the sick man allowed; I have revealed to no one a secret entrusted to me; I have given no one a fatal draught; no woman has ever brought about an abortion by my aid; nothing base has been committed by me in any house where I was practising; in short, nothing has been done by me which might be considered unbecoming an excellent and famous physician. I have always held up to myself Hippocrates and Galen as examples worthy of being followed by me, and the records of many other excellent men in the medical art have not been scorned by me. In my method of studying I have been so eager that no task, however difficult, could lead me away from the reading of good authors, nor the loss of private fortune, nor frequent journeys, nor yet exile, which, as befits a philosopher, I have thus far borne with calm and invincible courage; and the many students which I have thus far had I have always considered my sons, and have taught them very frankly, and have urged them to strive to conduct themselves like good men. I have published my books on medical matters with no desire for profit, but I have had regard for this one thing, namely, that I might, in some measure, provide for the health of mankind. Whether I have succeeded in this I leave to the judgment of others. At all events I have held this always before me, and have given it chief place in my prayers. Given at Thessalonica, in the year of the world 5319 [1559].

A few years later Amatus died and one of his friends, the Marrano Flavio Jacopo de Evora, composed a memorial to him in beautiful Latin verses to the following effect:

He who so often recalled the breath well-nigh gone from the dying, and was, therefore, beloved by kings and peoples, lies far from the land of his birth, beneath the dust of Macedonia! (Graetz's History, English edition, Vol. IV, p. 610.)

Such were the ethical ideals of the Jewish physician in the middle ages. Surrounded by charlatanry, ignorance, fanaticism and bigotry, suffering cruel persecutions, driven from place to place, they held fast to these high ideals, for nothing lower would have been in accord with their traditions and their religion.

APPENDIX.

It would be tempting to include what is referred to in numerous accounts as the "Prayer of Maimonides." This appeared, in January, 1863 (*Allgemeine Zeitung des Judenthums*), in a German translation under the title: "Daily Prayer of a Physician Before Visiting His Patients, translated from a Hebrew manuscript of a celebrated Hebrew physician of the 12th century." It is a very lofty and beautiful prayer. It has been published and republished frequently and it is ascribed to Maimonides[12] or to "a distinguished Jewish physician of the 12th century," in such works on medical history as Haeser (1875, Vol. 1, page 837), and in biographies of Maimonides (such as Pagel's: Maimuni als Medizin. Schriftsteller, 1908, p. 244). Professor Gotthard Deutsch of Cincinnati has given an interesting account of the wanderings of this prayer and has shown that "it is the work of Marcus Herz, of Berlin (1747-1803), the friend and physician of Moses Mendelssohn, and was translated into Hebrew by Isaac Euchel, who published it in the Hebrew periodical, "Ha-Meassef, Vol. VI, pp. 242-244, 1790."[13] On account of its intrinsic value, it is appended in an English translation.

Daily Prayer of a Physician.

Almighty God, Thou hast created the human body with infinite wisdom. Ten thousand times ten thousand organs hast Thou combined in it that act unceasingly and harmoniously to preserve the whole in all its beauty—the body which is the envelope of the immortal soul. They are ever acting in perfect order, agreement and accord. Yet, when the frailty of matter or the unbridling of passions deranges this order or interrupts this accord, then the forces clash and the body crumbles into the primal dust from which it came. Thou sendest to man diseases as beneficent messengers to foretell approaching danger and to urge him to avert it.

Thou hast blest Thine earth, Thy rivers and Thy mountains with healing substances; they enable Thy creatures to alleviate their sufferings and to heal their illnesses. Thou hast endowed man with the wisdom to relieve the suffering of his brother, to recognize his disorders, to extract the healing substances, to discover their powers and to prepare and to apply them to suit every ill. In Thine Eternal Providence Thou hast chosen me to watch over the life and health of Thy creatures. I am now about to apply myself to the duties of my profession. Support me, Almighty God, in these great labors that they may benefit mankind, for without Thy help not even the least thing will succeed.

Inspire me with love for my art and for Thy creatures. Do not allow thirst for profit, ambition for renown and admiration, to interfere with my profession, for these are the enemies of truth and of love for mankind and they can lead astray in the great task of attending to the welfare of Thy creatures. Preserve the strength of my body and of my soul that they ever be ready to cheerfully help and support rich and poor, good and bad, enemy as well as friend. In the sufferer let me see only the human being. Illumine my mind that it recognize what presents itself and that it may comprehend what is absent or hidden. Let it not fail to see what is visible, but do not permit it to arrogate to itself the power to see what cannot be seen, for delicate and indefinite are the bounds of the great art of caring for the lives and health of Thy creatures. Let me never be absent-minded. May no strange thoughts divert my attention at the bedside of the sick, or disturb my mind in its silent labors, for great and sacred are the thoughtful deliberations required to preserve the lives and health of Thy creatures.

[12] **An interesting analysis of this prayer is published by Kroner, in which he shows the harmony between it and the writings of Maimonides. (Ost und West, 1912, p. 745.)**

[13] **American Israelite, March 19, 1908.**

Grant that my patients have confidence in me and my art and follow my directions and my counsel. Remove from their midst all charlatans and the whole host of officious relatives and know-all nurses, cruel people who arrogantly frustrate the wisest purposes of our art and often lead Thy creatures to their death.

Should those who are wiser than I wish to improve and instruct me, let my soul gratefully follow their guidance; for vast is the extent of our art. Should conceited fools, however, censure me, then let love for my profession steel me against them, so that I remain steadfast without regard for age, for reputation, or for honor, because surrender would bring to Thy creatures sickness and death.

Imbue my soul with gentleness and calmness when older colleagues, proud of their age, wish to displace me or to scorn me or disdainfully to teach me. May even this be of advantage to me, for they know many things of which I am ignorant, but let not their arrogance give me pain. For they are old and old age is not master of the passions. I also hope to attain old age upon this earth, before Thee, Almighty God!

Let me be contented in everything except in the great science of my profession. Never allow the thought to arise in me that I have attained to sufficient knowledge, but vouchsafe to me the strength, the leisure and the ambition ever to extend my knowledge. For art is great, but the mind of man is ever expanding.

Almighty God! Thou hast chosen me in Thy mercy to watch over the life and death of Thy creatures. I now apply myself to my profession. Support me in this great task so that it may benefit mankind, for without Thy help not even the least thing will succeed.

PALÆOPATHOLOGY.*†

By Arnold C. Klebs, M. D., Washington, D. C.

Palæopathology is a term applied by Marc Armand Ruffer to recently developed methods of pathologic investigation in the realm of the very old. It is historical research because it endeavors to supply data in the evolution of mankind, not in the conventional sense, however, for its methods are those of direct and systematic observation. The adjective "prehistoric," used so often, would seem a misnomer, because the distinction of a history read in written records from one seen and studied in equally characteristic objects, chronologically determinable, is purely arbitrary and artificial and it would do no harm to drop it altogether.

The Greek prefix in "Palæopathology" may suggest a limitation of its scope to the era revealed to us in the fossilized forms of life. But such is not intended, although palæopathology has already found objects for research in this remote epoch. It is an American student, Professor Moodie, who is doing pioneer work in this field, by showing that the Mesozoon can yield most interesting pathologic and even bacteriologic specimens.[9, 10] Another American investigator, Dr. Aleš Hrdlička, has developed intensively the palæopathological side in his numerous explorations and studies of the aborigines on this continent. The establishment by him of a very remarkable exhibition of palæopathologic specimens in San Diego, which is probably unique of its kind, is a great credit to scientific enterprise in this country.

These efforts, as well as the subject itself, deserve more general attention. The literature on the subject, especially the foreign one, being scattered in publications not readily accessible, a brief review may not be out of place at a time when opportunities for similar research are increasing.

We may justly regard Rudolf Virchow as the founder of palæopathology. His deep interest in archæology and anthropology made it inevitable that in the objects which came to his attention the pathological features should not escape him. Many reports of these observations of his will be found among his writings and his masterful descriptions still merit careful attention. Several of his pupils, as well as other investigators in Germany and France, have added reports of various specimens. In France and in this country (Robert Fletcher[3]) the subject of ancient trepanation has particularly attracted students. But to coordinate such isolated efforts, more material was needed and especially competent workers in the field, to supervise the excavations, to examine and order the material according to fixed standards. Such larger opportunities were offered only in recent years by the various scientific expeditions to Egypt and especially by the well organized archæological survey undertaken by the Egyptian Government in 1908 and 1909, previous to the artificial inundations caused by the closing of the Assuan dam. From this undertaking, carried out particularly by Drs. Marc Armand Ruffer, G. Elliot Smith and Wood Jones, dates the establishment of palæopathology as a special branch of research.

It is of the utmost importance that the age of the objects to be examined be clearly determined. Amateur explorers have too often ignored this. The exploring physician has to become an experienced anthropologist and archæologist or cooperate with such. The type of mummification, the posture of the body in the grave, its orientation, the geologic and cultural strata, objects of adornment, clothing and other fabrics, pottery and weapons, are some of the features successfully utilized for the dating of the remains. Without such circumstantial evidence the excavated pathologic specimens have very slight scientific value. Previous interferences with these burial grounds present problems well nigh insoluble. Just as artistic and architectural relics have suffered more from the

* A bibliography of the subject will be found at the end of this paper. The numbers in the text refer to it.

† Read before a meeting of The Johns Hopkins Hospital Historical Club, November 13, 1916.

hands of earlier "investigators" and collectors than from the wear and tear of time, so also the human remains have suffered by this neo-vandalism. Sometimes greed but more often plain ignorance is at the bottom of these devastations of precious material. But the archæologist and anthropologist will also have to learn to take notice of the objects showing pathologic features and preserve specimens which at first sight may seem to present only unimportant alterations.

The state of preservation of the objects from the earliest burial grounds, those of the Stone Age for instance, is usually such that the examination requires special precautions. Anyone who has ever assisted at an exhumation of a palæolithic or neolithic skeleton will readily appreciate this. Only very rarely can the bones, let alone the whole skeleton, be removed from the earth *in toto*. Everything is so brittle that the slightest touch will often destroy the structural outline. Successive layers of earth and rubbish have to be removed with great care from around the bones. When once laid bare, an artificial humidity must be maintained, otherwise the whole structure would pulverize into nothing. The form of such a skeleton can sometimes be preserved only by plaster casts or photographs. These difficulties obtain practically through the whole district of central and southern Europe, where the geologic history of living nature has been more intensively studied than anywhere else. Still, even here some interesting palæopathologic observations have been made.

So far, chiefly Egypt and Peru have furnished the more important specimens, but undoubtedly there are other regions yet unexplored, especially in the immense territories of Central Asia, Mesopotamia, the Irak and Central America, where important discoveries are to be expected. To make broad generalizations from the findings made so far would be premature, but it seems that there are some important differences between the pathology of those remote days and ours. Already we can faintly trace in these relics the primitive state when man's fate was sealed almost exclusively by injury or old age, gradually developing to that of the more complex nosology of our days. Sometimes we are even allowed to study the results of early therapeutic efforts. Some of the early surgical operations, trepanations for instance, of which we find such striking traces, propound riddles difficult to solve, others permit us to admire a great skill and the evidences of prolonged nursing care which we are astonished to encounter among primitive peoples. Again, in some specimens we find alterations which bear no resemblance whatever to such as are found to-day.

In order to give a concrete view of the possibilities of palæopathologic research I shall now review, under separate headings, some of the more recent findings illustrating the pathology of past ages.

Bone Lesions.

The most frequent bone diseases among ancient peoples seems to have been *arthritis* and *osteitis deformans*. Wood Jones[1] includes within this term most of the hyperplastic bone changes which have been and still are described as rheumatic or rheumatoid, since Adams in 1836 introduced the confusing term "rheumatic gout." Very justly Jones remarks that there is nothing to be gained by an etiologic nomenclature so long as we have so little definite knowledge about the causes. He therefore groups all of these changes under the term *osteitis*. Their clinical entity was established first by Haygarth in the 18th century ("nodosities of the joints") as distinct from gout and rheumatic fever. The latter, the acute, progressive, polyarticular arthritis was not found in ancient skeletons, and of gout only one case, a very interesting one, chemically determined as such, was seen in a mummy from an early Christian cemetery.

Osteitis Deformans.*

Chiefly according to their localization the alterations encountered are distinguished as arthritis, spondylitis or simple osteitis. They are characterized by evidences of inflammation and the superposition of new bone tissue, often of fantastic proportions, regular stalactites, such as are rarely found nowadays. Sometimes there is some bulging and bending of the bones which ally these conditions to osteomalacia. The absence of ulcerative, necrotic defects can alone allow the important differentiation from syphilitic and tuberculous bone diseases. That this is not always easy will be shown later. Osteitis deformans must be considered the disease *par excellence* of the ancient Egyptian (Wood Jones) and probably that of all ancient peoples, to judge from reports of many other observers. In Egypt the evidences of its prevalence go back to predynastic periods. In the oldest times it appears that no single adult escaped some of its troublesome manifestations. Wood Jones is inclined to explain it on the basis of environmental causes, especially by the wet occupation in the Nile and subsequent exposure to the excessive heat and cold of the Egyptian climate. These same conditions existing to-day as then, while the frequency of the disease has distinctly diminished, rather tend to disprove Jones' theory. Neither can racial factors be made responsible, for the changes are found in a great variety of peoples. At any rate, a meaningless nomenclature will not hide our ignorance on the subject. Whether these processes can be explained, according to the tendency of the day, as due to infection is as conjectural as their specific allotment to tuberculosis, continuously insisted upon by Poncet on clinical grounds.

When we examine these bone changes, especially those of spondylitis, they present indeed striking resemblances to tuberculous bone disease. Closer investigation shows, however, the absence of distinct necrosis and medullary foci. Some resorption of bone may have taken place here and there, the intervertebral discs may have wasted under compression in kyphotic and lordotic deformation of the spinal column due to the unilateral fusion of the vertebræ. These are all features which, in spite of superficial resemblances, exclude the

* Sir James Paget restricted the use of this term to a disease which now bears his name but which is better described as chronic hypertrophic osteomalacia.

diagnosis of tuberculosis, at least so far as this term expresses our morphologic and bacteriologic notions of the disease. The spondylitic lesions seem always to precede the other localizations of the disease (metastases?). The lumbar column is most frequently affected and practically no archaic man seems to have been entirely exempt. In this connection, it is interesting to note that the derivative for "old age" in hieroglyphic writing is the picture of a deformed man (Ruffer). From the atlas to the coccyx no part of the spinal column (and as a matter of fact of the whole skeleton) was found unaffected. In one case from the third dynasty (*ca.* 3800 B. C.) and one from the Roman period (200 A. D.) the whole spinal column was one rigid bony mass. Pathologically it is the intensity of the process rather than anything else that distinguishes the ancient disease from the modern. Similar arthritic changes are found in all the other joints (somewhat less frequently in the knee) and it is notable that the accompanying hyperostoses are often more conspicuous in those parts of the bones which are at a distance from the joints. Roughened joint surfaces tending towards ankylosis are the rule and one sees rarely cases of the eburnation of the joint surfaces, so typical to-day. Humerus, ulna and femur present sometimes monstrous deformities, less so the phalanges of hands and feet where, however, the typical nodosities described by Bouchard (in connection with chronic dilatation of the stomach) were observed by Ruffer and Rietti.[10] Whether the very peculiar deformations noted in the bones of the hip-joints of Peruvian origin by Hrdlička [8] are essentially different, remains to be seen.

Tuberculosis.

As already said, evidence of a marked prevalence of bone tuberculosis in the ancient Egyptian and also in the Peruvian seems to be lacking. The subject of pre-Columbian tuberculosis in North America cannot be profitably discussed on the basis of the available material. There is one carefully described case of supposed tuberculous spondylitis from a neolithic burial ground near Heidelberg (Bartels). But the vertebræ in the skeleton here examined were in such a state of disintegration that the conclusions arrived at do not seem altogether convincing. Poncet also described as tuberculous certain bone lesions found in a mummified monkey from a Theban cemetery (1000 B. C.). More convincing is the case of Potts' disease discovered by Smith and Ruffer [9] at Philae in the mummified body of a venerable priest of Amon, dating from the 21st dynasty. Here, not only the very pronounced kyphosis traceable to the necrosis of one or two vertebræ, but the former site of a psoas abscess could be demonstrated macroscopically and microscopically. The features revealed in this case led to the discovery of a whole series of others in the same neighborhood and to the hypothesis of an Egyptian health resort, a sort of sanatorium for the tuberculous, in charge of the servants of the "veiled deity"—a romantic supposition, but hardly provable.

Palæopathology gives only scant information about the possible prevalence of other forms of tuberculosis. Pleural adhesions were not infrequently met with and may point to pulmonary tuberculosis. This disease we have come to consider as the disease *par excellence* of civilization and especially of indoor civilization, and the theory of the increasing immunity against it among peoples longest accustomed to in-door conditions might well find strongest support or disproval from palæopathological research. The apparent infrequency of bone tuberculosis naturally does not dismiss the question about the incidence of other forms and it would be indeed erroneous to conclude that the ancient Egyptian was free from consumption which we encounter in early medical literature. The possibility that the manifestations of the disease may have altered within long epochs cannot be altogether disregarded, inasmuch as the great variability, at least in intensity, is well recognized.

Osteoporosis.

Under this name, structural alterations in cranial bones of young individuals, apparently without counterpart in modern pathologic experience, have been frequently encountered and described by observers in widely separated districts, as for instance Egypt and Peru. They seem to have nothing in common with those changes now found in bones of the very young or old, described by pathologists under the same heading or as *fragilitas ossium*, neither do they resemble the porosities one observes at certain stages in the hyperostotic accretions of bones in syphilitic disease. Two different forms seem discernible, one which is characterized by circumscribed patches of porous osteophytes, the other in which the porous condition prevails without marked osteophytic proliferation, but also without any evidence of bone necrosis. Strikingly characteristic, as pointed out by Hrdlička,[8] is the localization of the patches in symmetrical regions of the skull and their confinement to those parts of the bone only which do not give attachment to muscles. Most frequently the osteophytic form is found on the roofs of the orbits (the only one described by the Egyptian observers); next in order come the frontal, parietal and occipital bone, and less frequently the wings of the sphenoid, parts of the temporals, and certain other bones of the base. There is no evidence that these formations have materially interfered with the well-being of the individuals affected. The findings so far do not allow the artificial construction of a clinical picture, distinguishing stages of active disease and recovery. As a matter of fact, it seems doubtful whether these findings allow us to speak of a disease at all, and conjecture about its toxic, nervous or what-not origin.

Rachitis and Syphilis.

Rickets, as defined pathologically to-day, does not seem to have been prevalent among archaic people. At least the characteristic lesions of the thoracal skeleton, the pelvis and the extremital bones (epiphyses) have not been found so far, with the possible exception of *coxa vara* conditions where, however, the bending of the femoral neck might be explained as a partial manifestation of the osteitis deformans which is

always present in these cases. Elliot Smith is inclined to consider certain distorted bones as evidence of rachitis. These mainly negative results cannot fail to astonish, because we have other evidences which suggest that rachitis did exist. I will only recall the frequent pictorial representation of deformed dwarfs and pygmies, also the bowlegged god *Bes* and the rachitic child on amulets of the Saitic-Persian period (Berlin Museum: von Oefele).

Syphilis, which we know to leave extensive and typical bone lesions, ought to be easily discernible in ancient bones, if the disease was at all prevalent. One remembers undoubtedly the reports which appeared at more or less regular intervals in our literature, about bones presumably pre-Columbian, exhibiting unmistakable signs of syphilis. Dr. D. S. Lamb,[7] who is the custodian of a number of these interesting specimens in the Army Medical Museum at Washington, has reviewed the whole subject, so that I need not enter here into details. There is no doubt that some of the specimens (especially two skulls described as having belonged to prehistoric Aleutians of Chermoffsky in Alaska by their discoverers T. H. Bean and W. H. Dall) show typical syphilitic lesions; less convincing are those on some long bones and still less some so-called necroses which are undoubtedly postmortal changes. But the real difficulty with these findings—and Virchow called attention to it at the time—is that of dating them accurately. It is also a very precarious business to make a diagnosis from the alterations in some isolated bone. This is only possible when the lesion happens to be in an unmistakably typical stage. The great bone defects caused by the breaking through of medullary gummata, especially in the cranial bones, without noticeable hyperostosis, are very characteristic but error has to be guarded against, for small gnawing animals are known to produce very similar destructions in the buried bones (Virchow, G. Elliot Smith). Really pathognomonic in dry flat bones Virchow considers only those typical marks left by the cicatrization of a gummous peripheral osteitis, a condition first described by Bertrandi (1723-1765) as *caries sicca*. Traumatic or simple osteitic or osteomyelitic processes (especially those observed on the skulls of people who customarily carry burdens on their heads) may simulate conditions of syphilitic origin but never this *caries sicca*. Smith lays great stress on the corroborative value of changes found in the teeth. At any rate we may safely conclude that the whole subject of the pre-Columbian origin of syphilis is still *sub judice* and that from careful palæopathological research in the future, more than from anything else, a solution may be expected.

Other Bone Lesions.

The teeth of the ancient Egyptians, like those of archaic people generally, are usually found in a state of excellent preservation. The attrition affects evenly the biting edges and surfaces and there is practically no deposit of tartar. In part this is probably due to a coarser kind of food than the one we are accustomed to. Gradually, however, conditions change to those closely approaching ours, as evidenced in the skulls from later burial grounds. Here we find all the reminders of painful days in the form of dental caries, periodontitis and suppuration. Curiously enough no evidence of dentistry is found, not even that of tooth-pulling. Only one artificial tooth was seen and the gold wires wound around some teeth, claimed to be some orthodontal device, are now regarded as mere objects of feminine, or perhaps, male coquetry. Of interest is also a case of great hypertrophy of the middle turbinated bone with complete occlusion of the nasal passage (Ruffer). We have records only of few bone tumors. Hrdlička mentions the frequent occurrence of small osteomata in the auditory meatus and Ruffer[11] described a larger tumor, probably an osteosarcoma, of the pelvis (250 A. D. Roman).

Injuries, Fractures and Dislocations (Sepsis).

The evidences of trepanations on skulls of ancient or primitive peoples have attracted probably the most widespread attention. A surplus of newer material precludes its discussion here, though its real meaning is not yet clear and ought to offer an interesting field for further research.[3]

The effects of injuries, whether accidental or purposive (battles, executions, etc.) can be observed in ancient bones in great variety. The Egyptian findings analyzed by Jones[3] and compared with modern conditions, as illustrated by the reports of the out-patient departments of hospitals in New York and London, form an interesting commentary on sociologic treatises, but it would lead too far to enter into this aspect here. Two facts seem to stand out prominently in the whole series: the almost entire absence of sepsis and a very pronounced tendency to natural repair. But some fractured bones had to be set artificially and a study of some of the healed fractures reveals a very high degree of skill, the variations of which can be traced in the several cultural epochs. The ancient bone-setter like the modern, saw his ideal in the avoidance of any deformity and the shortening of limbs, and we can verify his success in some of the healed bones by a comparison with the corresponding bone of the same skeleton. Of course great deformity and then always an abundant hyperplasia of bony tissue, as observed in fractured limbs of animals, are also found in the human remains, but this is by no means the rule. From the 5th dynasty on, we learn that splints were applied in cases of fracture, and some were found still *in situ* on the mummies. But we also know that other mechanical appliances must have been employed for the treatment of fractures when splints were not applicable and, in this direction, some of the findings corroborate directly the information we have from the literature. The collection of ancient surgery, based on the Hippocratic treatise on joints and commented upon by Appolonius of Kitium (1st century B. C.) is preserved in a precious illustrated Greek codex of the 10th century in Florence. It inspired several surgical works of the 16th century (Guido Guidi, Rabelais, Ambroise Paré *et al.*). In this collection we can see some of these ingenious appliances as used by the Greeks but very likely employed long before by the Egyptians.

DISEASES OF THE SOFT TISSUES.

As Ruffer [1] has pointed out, the tissues of those bodies which were simply buried in the sterile, dry sand of Egypt, with or without the addition of salt, are the ones best suited for microscopic examination. The Egyptian undertaker, the *paraschist*, embalmed the bodies without the slightest regard to the interests of future investigators. He usually managed to destroy or remove all the internal organs, so that bodies, from the periods when his art was particularly flourishing, *i. e.*, the New Empire, furnish only the scantest material. None the less interesting records have been obtained by the special methods devised by Ruffer and his associates. I shall refer, however, only to a few of the more striking findings, especially to that of the discovery of calcified ova of the schistosoma hæmatobium and the arterial lesions.

Bilharziosis is still one of the most distressing and destructive diseases in Egypt and its demonstration in those remote periods offers, therefore, a subject of the greatest interest. The disease can very probably be identified with the ããã disease of the Ebers and Brugsch papyri, in which it is stated that it was caused by the worm *Nelta*. Now, as Pfister has shown, the probability of this identification is greater than that also attempted—with Egyptian chlorosis, an affection due to the activities of the nematode *Ankylostoma duodenalis*. Two reasons speak for it: First, the trematode causing bilharziosis is somewhat larger than the ankylostoma and secondly, the most striking symptoms of bilharziosis, the hæmaturia and the typical local manifestation (tumefaction of the penis) would naturally have led to the introduction of a pictorial phallus into the hieroglyphic determinative for the ããã disease (surely not so much the sexual impotence subsequent to ankylostomiasis, as has been advanced by Joachim).

The arterial lesions found have led to some interesting considerations.*

Most important among these are the evidences of atheroma. Shattock initiated the investigations by examining microscopically the aorta of King Minephthah (*ca.* 1350 B. C.) in 1909 and very soon after Ruffer [2] evolved his excellent technic with which he searched a great number of mummies from the 18th to the 27th dynasty (1580-527 B. C.) and the time of the Persian Conquest (500 B. C.). The fact brought out by these investigations is the astonishing frequency of arteriosclerosis and the extent it reached in some individual cases. Rarely was the condition absent in older individuals. In some cases Ruffer found the arteries transformed into rigid "bony" tubes down to their minute ramifications. After decalcification and staining (Van Gieson) he obtained very interesting sections in which the course of the disease could be studied almost as well as in a fresh specimen. Nothing in particular distinguished the histological findings from those observed to-day, but it is highly interesting that the arterial coats and the annular fibers were still clearly to be distinguished in these 3000-year-old specimens.

In view of the many modern speculations regarding the etiology of arteriosclerosis, it may be of interest to consider the question in the light of these venerable testimonials. Unfortunately, we cannot expect any illumination about blood pressure, a subject to-day occupying the center of the stage. Tobacco and syphilis we also have to exclude. The strenuousness of modern existence may or may not have had its counterpart in Egyptian life and Ruffer remarks very pointedly that we certainly cannot complain of overwork when we compare our activities with those of our ancestors. Meat diet and luxury, another presumed cause, probably existed more or less in all those Egyptian epochs, although meat was surely not the main article of food, as is to be seen in contemporaneous pictures of feasts in which vegetables always abound. Ruffer also found arteriosclerosis equally prevalent among the high-living priests and priestesses of ancient Deir el-Bahari as among young, modern Egyptians who eat meat but rarely. Neither can strenuous muscular exercise have been a causative factor in these same priests who were not likely to indulge in sports or hard manual work. There remains alcohol! When we remember Herodotus' report about the obligatory drunkenness in deliberative assemblies of the Persian legislators and similar references to vinous habits in Egyptian documents, we cannot adduce these facts for an etiologic comparison with modern conditions until prohibition has become a more solidly established institution. It might, however, help those who do not believe in the responsibilities of alcohol in this matter, to know that Ruffer examined the bodies of a number of Mussulman pilgrims who never had touched a drop of alcohol and found arteriosclerosis very frequently.*

Palæopathology is only in its very beginnings. The comparative scantiness of facts so far brought out and the difficulties of the research ought not to hinder its energetic pursuit. In the concatenation of specialized scientific inquiries it forms a precious link that well merits more widespread attention. It must be recognized that injury and disease have played an important part in the history of mankind. We need only consider what definite influence they exert in our individual lives, what profound social upheavals were brought about through the incidence of epidemics, less perceptibly perhaps but none the less strongly, through widespread chronic ailments, through professional diseases, how whole districts and countries were forsaken because disease made them uninhabitable, how diseases affecting early childhood and others producing sterility led to the gradual extinction of whole peoples. And also, as regards the microorganisms that we

* In passing it may be mentioned that examination has shown that the blood-vessels of some mummies had been injected with some substance not yet identified, but surely not bitumen. Further investigations on this subject may throw suggestive sidelights on the physiologic knowledge of the paraschists. The existence of aneurysm was suggested by the finding of one large opening at the base of one skull, due most likely to pressure erosion from an aneurysm of the internal carotid artery.

* For completeness' sake I must add that Ruffer discovered, in one mummy of the 20th dynasty, a skin eruption resembling microscopically and macroscopically that of variola, and that the detection in other cases of a hypertrophy of the spleen suggested the existence of malaria in those times.

make responsible for so large a share in our physical troubles, must it not be assumed that they also traverse evolutionary stages in their fight for existence in the same way as other forms of living substance? We may find evidence of varying virulence, of their producing in one epoch recognizable though negligible diseases, in the other disastrous calamities. For the grasp of such problems, the study of disease as it appears to us now does not suffice, the traces left during immense periods of time have to be taken into account and it is just in such questions, not approachable by other methods, that palæopathology in time to come may furnish important solutions.

The search for evidences of a primitive therapeusis may bring forth material which may throw a light on the earliest origins of medicine and on those very actual questions about the spontaneous, local origin or the spread of culture over the earth, from one particularly advanced center. One of the pioneers in palæopathologic research, Dr. G. Elliot Smith, ardently defends the latter alternative. He holds that all evidence of culture in the various lands of the earth, no matter how far distant they may be from each other, can be traced to the direct influence of emissaries from the great civilization built up in Egypt between 4000 and 900 B. C. The theory is based on some striking resemblances of certain rather bizarre cultural features (the so-called heliolithic culture-complex: suncult, mummification, huge buildings, tattooing of the chin, svastika emblem, etc.) in widely separated districts. These resemblances are indeed striking and forcibly suggest an interrelation of these people during some remote epoch, but they hardly justify the summary denial of the possibility of the spontaneous, independent rise of a primitive culture, based on the innate tendency of man to improve his surroundings, to avoid or alleviate suffering or to correct physical defects. This must be considered as due to instinctive efforts, to an "*a priori synthesis*" in William James' sense, which can be observed among all primitive peoples, even among animals to a certain degree, efforts which necessarily must resemble each other somewhat; such as we should probably find among peoples of some other planet beyond the possibility of receiving suggestions from Egypt or elsewhere. Although "originality is certainly the rarest thing in this world" [B. Laufer; Jade, 1912, p. 5], and although in a tolerably advanced stage of civilization it will be almost impossible to distinguish clearly between what is original and what is borrowed in medical practice, anything that will make us acquainted with the early rise and evolution of therapeutic procedures may carry valuable lessons. This is a side-issue of palæopathologic research, but not the least interesting one.

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ABSTRACTS OF PAPERS

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A COMPARISON OF THE PERMANENCE OF FREE TRANSPLANTS OF BONE AND CARTILAGE. AN EXPERIMENTAL STUDY.

By JOHN STAIGE DAVIS, M. D., F. A. C. S., Baltimore, Md.

(Abstract from Ann. of Surg., 1917, Feb., p. 171.)

Introduction.—The appearance of a number of clinical papers advocating the transplantation of bone for the relief of saddle nose has interested me, because I had come to the conclusion that cartilage was the best material to use in such cases. As there seemed some difference of opinion as to the relative stability of bone and cartilage transplants, I carried out the following procedures on dogs, in order to clear the matter up, at least from an experimental standpoint.

In order to produce conditions which would be somewhat similar to those in actual clinical practice, I transplanted the cartilage and bone, each 2 cm. long, so that one extremity of the transplant was in close contact with a denuded portion of a membranous bone, while the remaining portion extended into the soft parts. Autotransplants only were used.

EXPERIMENTS.—*Group 1. Transplantation of cartilage with its perichondrium intact, and rib without periosteum.*—Six experiments. Specimens were examined after 24, 25, 85, 223, 576 and 582 days. In each the cartilage was found apparently intact, and 2 cm. in length. After 24 and 25 days there was little change in the length of the bone, although beginning absorption was noted. In the 85-day specimen there was a somewhat dense outgrowth of bone from the skull about the impinging portion of the transplant. This appeared rather excessive, when compared with that in the other specimens, and might have been caused by a slight localized infection. There was marked evidence of absorption, although the bone was still 2 cm. in length. After 223 days no bone could be found, either by X-ray or by dissection. In the 576-day specimen a very small irregular spicule of bone was found projecting from the skull. It measured 2 mm. in length and breadth, and 1 mm. in thickness. In the 582-day specimen an irregular spicule of bone, 0.5 mm. long, projected from the parietal bone.

This group seems to show that under the same conditions transplanted cartilage and spongy rib bone behave quite differently. The cartilage retains its original size, while the bone in the shortest experiment shows beginning absorption, and this progresses as time goes on. It is difficult to say why the bone in the 223-day experiment should have disappeared, while evidences remained of the transplant in experiments observed for more than twice that length of time.

Group 2. Cartilage with one-half of its perichondrium, (lengthwise), and rib without periosteum.—Four experiments. Specimens were examined after 44, 125, 374 and 505 days. In each the cartilage was found to be the same length as when transplanted. After 44 days the bone was a scant 2 cm. long and showed evidences of absorption. After 125 days the bone was 1 cm. long, very thin and nearly absorbed. After 374 days only a thin spicule of bone, 8 x 2 mm., remained. After 505 days a thin fragment, 7 x 2 mm., remained.

Group 3. Cartilage without perichondrium, and rib without periosteum.—Two experiments. Specimens examined after 165 and 332 days. In both the cartilage was found to be 2 cm. long and apparently intact. In the 165-day specimen the bone had disappeared. After 332 days the bone was thin and flexible, and measured 7 x 1 mm.

These groups again emphasize the tendency of bone to be absorbed and of cartilage to retain its original length and thickness, even though partially or wholly denuded of its perichondrium. It is impossible to say why one of the rib transplants had disappeared in 165 days, while thin fragments of bone, showing all the signs of degeneration, were found 332, 374 and 505 days after transplantation.

Group 4. Cartilage without perichondrium, and rib with strip of periosteum.—Four experiments. Specimens were examined after 13, 26, 49 and 56 days. The cartilage remained unchanged in each. After 13 days there was no change in the size of the bone. In the 26- and 56-day specimens the bone was found to be 1.6 cm. long, and in the 48-day specimen it was 1.4 cm. long.

This group again shows the tendency of bone to absorb, in spite of the presence of undisturbed periosteum, and the cartilage to be unchanged, even though the perichondrium is removed.

Group 5. A section of fibula, with periosteum, and a similar section without periosteum, were transplanted as in previous experiments.—Three experiments. The sections of fibula to be compared were of equal length, and varied between 1.4 and 1.8 cm. in the different experiments. Specimens were examined after 305, 328 and 388 days. In each the section of fibula without periosteum had been absorbed. In the 305-day experiment the section of fibula with periosteum, which was originally 1.8 cm. long, measured 5 mm. long by 1 mm. at its widest, and was thin, irregular and flexible. In the 328-day experiment the transplant, which was covered with periosteum and originally was 1.75 cm. long, measured 8 x 1 mm., and was thin and flexible. After 388 days the fibula, covered with periosteum, which was originally 1.4 cm. long, measured 7 x 1 mm., and was thin and flexible.

This group shows that the hard bone of the fibula is absorbed, as well as the more spongy bone of the rib. It also confirms experiments previously reported, which showed that a bone covered with periosteum is more resistant to absorption than denuded bone, but that in time it also will be absorbed.

Remarks.—It has been often demonstrated that free bone, either with or without periosteum, when transplanted into soft parts, without any particular function, will eventually be absorbed. From these experiments this also seems to apply to

free bone transplants with one end in contact with denuded bone, as in no instance, where any considerable time had elapsed, was the transplant found holding its own against absorptive processes. In the experiment of longest duration only a tiny spicule of bone remained projecting from the parietal bone, and it is obvious that this remaining portion would have been insufficient had the original transplant been used as a supporting framework.

The cartilage in each experiment showed no signs of absorption and was normal in appearance, even when entirely denuded of perichondrium. In no instance was there any increase in the length of the cartilage.

The healing was reactionless, and the cartilage did not act as a foreign body. The measurements of the cartilage differed very little, if at all, from those taken at the time of transplantation. On section the cartilage appeared normal and seemed well nourished.

Conclusion.—These experiments show that transplants of free cartilage were unchanged during the length of time under observation, while free bone transplants under exactly the same conditions had either disappeared, or showed marked degenerative processes.

THE SIGNIFICANCE OF THE LUNULA OF THE NAIL.

By Montrose T. Burrows, M. D.

(From the Department of Pathology, The Johns Hopkins Hospital and University, Baltimore, Md.)

(Abstract of article in The Anatomical Record, 1917, XII, No. 1.)

The nail is one of a few of the parts of the body which continues to grow throughout the whole life of the individual. In connection with the work on the mechanism of the cellular growth in the tissue culture, the author has undertaken a more careful study of this organ, hoping in the finer details of its structural peculiarities to find something of further importance for the better understanding of the conditions which regulate the growth of cells and tissues in the organism.

During the early part of this study the author has noted certain peculiarities in the structures of the lunular portions of the nail which, as far as he has been able to ascertain, give for the first time a definite explanation for the opacity of this region. The matrix throughout the lunular area does not adhere tightly to the underlying connective tissue, but lies merely in contact with these underlying structures, so that throughout this whole region possible reflecting surfaces are formed. In the outer portions of the nail the matrix is firmly attached to the underlying connective tissue. The connective tissue in this outer region is richly supplied with capillaries. The connective-tissue fibrils pass either directly from within outwards or obliquely outwards to end in and become attached to the basement membrane or the border of the cells of the matrix. Throughout the region of the lunula they take a quite different course. At the border of the matrix they run parallel to it; here they form a thin, dense layer or membrane. The connective tissue of this region contains few capillaries. These are in large part arranged in a network within and on the surface of this thin superficial connective tissue membrane.

In the modern textbooks of anatomy the opacity of the lunula has been ascribed to a peculiar opacity of the nail proper or of its matrix in this region. We have studied carefully by transmitted light many nails that have been removed together with their matrix. In no case, including a large majority of those nails which had been previously fixed and hardened, has the part of the nail corresponding to the lunula been found to be more opaque than other parts of the nail; quite to the contrary, it has been found to be more translucent.

Again, we have studied carefully a possible relation between the decrease in the number of capillaries in the connective tissue of the region of the lunula and the opacity in this region. These studies have yielded, however, little evidence that would indicate any such relation. First, it has been found that the change in the density of the capillary bed of the outer portion of the nail to that of the lunular portion at the distal margin of the lunula is never as abrupt as the boundary line of the lunula demands. Further proof against this peculiarity playing any important rôle in conditioning the opacity is given by comparing the appearance of the lunular areas with a portion of the body from which the blood has been removed by pressure. The lunula has a definite opacity, whereas that portion of the body from which the blood has been removed has a greyish translucence.

In absence of other possibilities, the author has been led to believe, therefore, that the lunular opacity is the result of a reflection of the light at the surfaces of the junction of the matrix and the connective tissue of this portion of the nail. In the outer portion of the nail where the matrix adheres closely to the underlying connective tissue the light is transmitted directly to the capillary bed giving it a characteristic pink color; while in the region of the lunula the well-formed non-adherent surfaces of both the connective tissue and the matrix reflect the light. More direct proof of this assertion may be readily obtained by pulling a portion of the body of a living nail loose from the connective tissue, thus forming such a surface in this region. During the past few weeks the author has been performing work which has led to the production of this injury. In every instance, in which it has occurred, the detached portion has shown an opacity quite indistinguishable from the opacity of the lunula of the same finger. It is of interest, however, that unless the injury is extensive the nail will again, after a few hours, become adherent and assume its former pink color.

The decrease in the capillary bed of the lunular area has been described (Poirier and Charpy, Traité d'anat. hum., Paris, 1901). No one, on the other hand, so far as the author has been able to determine, has described the peculiarity of the adhesion between the matrix and the connective tissue in this region, or the relation of the peculiarity in structure to the lunular opacity. It will be of further interest to ascertain whether many of the pathological opacities of the nail are not the result of similar changes,* and to study more carefully the

* This explanation for these opacities has already been suggested by several different authors.

conditions which lead to the adhesion of the matrix in the outer portion as contrasted with that of the lunular zone, and the general changes in the connective tissue and in the arrangement and density of the capillaries in these two regions. In the analysis of these latter conditions, we believe, we shall find many important facts related to the nature of the mechanisms of growth and differentiation of the tissue cells.

THE TISSUE CULTURE IN CANCER.

By MONTROSE T. BURROWS, M. D.

(From the Pathological Laboratory, The Johns Hopkins Hospital and University, Baltimore, Md.)

(Abstract of paper delivered before the Second Pan-American Scientific Congress, Washington, January 6, 1916.)

(To be published in Trans. Second Pan-American Scientific Congress, 1917.)

Cancer considered in its general aspects is a condition, although unique, which must be understood only by the use of those same methods by which we are eventually to understand normal and other pathological processes. The important problem in pathology and in biology is the structure and metabolism of normal body cells. The question in cancer is whether the cancer cell is a normal cell responding to a peculiar environment or whether it is a cell whose metabolism is such that it can grow in an environment where other cells cannot show these changes.

At one time it was supposed that the cycle of the life of the organism was the cycle of the life of the cell. At the present time, however, this particular view has been largely discarded and it is now held that not only is the body controlled by its cells, but that the cells are likewise controlled by the body. There is a mutual interrelation between the whole and its minute parts. Each and every activity of the cell is a response on its part to some external stimulus. Each and every activity of the whole is the result of the coordinated activity of its parts. The cessation of the growth of many cells at maturity does not represent a loss of the property of these cells to proliferate, but is the result of some kind of a change either in the organization of the cell or in the parts about it.

Although it has been assumed that this peculiar type of regulation of growth and other changes in the body cells is the result of peculiarities of their structure and metabolism, and that it must be solved by direct analysis of the mechanisms peculiar to each of the various activities of these cells, up to the time of the development of the tissue culture method no means for such direct analysis had been devised. The tissue culture method has become important in cancer as in the study of normal and other pathological processes in that it allows one to study directly the reactions of these various cells in a restricted and analysable environment.

During the last few years the author has studied by this method several different kinds of normal and cancer cells. Through this study he has been able to demonstrate directly that the normal cells of the organism are essentially fluid systems and that the organization peculiar to their various activities, such as growth, movement, differentiation, function, etc., are differential surface tension phenomena, regulated by the organization of the environment and the peculiar properties of certain of the substances formed in their oxidation reactions. The organization peculiar for each of these activities is not a cellular but a tissue organization. Thus it is seen how these cells may, under the influence of changes in their environment, undergo changes in form and activity.

A further careful study of oxidation in these cells has been made. Oxidation in these cells is a simple, incomplete, chemical reaction. CO_2 and another or other substances are formed. Certain of these compounds formed are insoluble in the circulating body fluids, serum, salt solution, etc., but soluble in various body colloids, such as fibrin, dead cells, etc. In the presence of food and oxygen this oxidation reaction can continue only so long as these products remain below a certain concentration. When this concentration is attained about the cells all activity ceases. For growth to take place in these cells a special mechanism for removing these products must be available, that is, it can take place only when the cells are brought into contact with certain colloidal materials having the property of absorbing these substances; and it continues until their concentration in these colloids reaches a certain concentration; then an equilibrium is established. Thus, we can see how the coagulable exudate in the wound forms the stimulus for growth and how growth ceases at the establishment of continuity of the part or how it fails through a failure of the formation of the exudate.

A careful study of the nail shows that it has a special mechanism for supplying colloidal materials and removing them continuously from the growing cells. The rhythmically contracting heart muscle cell has an electro-mechanical structure capable of splitting these substances into simpler compounds which are soluble in the circulating body fluids. The energy is transformed into work in these cells through the fact that the primary oxidation products decrease surface tension whereas their split products increase it.

Cancer cells have not been found to be different from actively growing normal cells. The study of them has, however, been so far limited.

SOME FACTORS REGULATING GROWTH.

By MONTROSE T. BURROWS.

(From the Department of Pathology, Johns Hopkins Hospital and University.)

(Abstract of article in The Anatomical Record, 1917, XI, No. 6.)

The problems under consideration in this paper are (1) the nature of the immediate conditions which lead to the failure of scar formation in many wounds or following many extensive inflammatory processes and (2) the general nature of the conditions which inhibit or allow the growth of connective tissue. It is well known that the most extensive inflammations of epithelial surfaces, as pneumonia, are most often followed by complete healing, while inflammations of the deeper connective areas are most frequently followed by the formation of a scar. In cancerous processes the connective tissue cells grow wildly at the expense of other parts.

Hertzler, a few years ago, came to the conclusion that the fibrinous exudate which forms in a wound, is the direct stimulus for the growth of the connective tissue cells. He noted that skin grafts take only when they become embedded in a layer of coagulable exudate. He also thought that the fibrin fibrils were transformed directly into the extracellular connective tissue fibrils. He had come to this last conclusion by means of a careful chronological study of intestinal adhesions and wounds induced by mechanical means in young rabbits of the same litter. He noted that previous to healing the fibrin is laid down in the form of fibrils. Connective tissue cells migrate among these fibrils. At a later period he found the fibrous tissue fibrils to occupy the same position and have the same arrangement as the fibrin fibrils. The wounds and adhesions had been removed at regular intervals, sectioned and stained. He was unable to see any evidence of the disappearance of fibrin, and the laying down of the connective tissue fibrils. Similar experiments were also made with wounds. In the summer of 1908, the author had the opportunity to study these experiments with Dr. Hertzler.

In the early studies of tissue culture made at Cornell University Medical College, it was noted that the fibrin fibrils in many of the cultures, after a considerable growth of connective tissue cells, stain the characteristic pink color, of white fibrous tissue with van Gieson stain. These observations were communicated to Dr. Hertzler, who reported them with his own studies ('13). Recently, Baitsell ('16), in Harrison's Laboratory, has made similar observations in tissue cultures. He did not observe the characteristic color reaction with the van Gieson stain.

Whether or not these pink-staining fibrils that had been observed in the tissue culture could be considered as true fibrous tissue, or merely structures simulating these fibers in their ability to absorb dyes, was a problem of interest. One of the objections to accepting them was the inconstancy of the appearance of pink-staining fibrils in many of the cultures.

In later studies of the growth of tissue *in vitro* several facts have been found, however, which would tend to substantiate this particular view. The first is that clot contraction or the formation of fibrin fibrils in the cultures of chicken tissue in plasma occurs only in the presence of connective tissue cells. Chicken plasma, when carefully prepared, free from previous tissue contamination, clots with the addition of a fragment of tissue to form a practically structureless jelly-like mass which has the same volume as the original fluid plasma. Any type of tissue conditions this primary clotting. In the presence of living connective tissue cells the clots later undergo contraction, while in the presence of epithelium they may undergo contraction but later liquefaction. Leucocytic or lymphocytic cells cause only slight liquefaction of these clots and very little, if any, contraction.

The second fact is that this contraction takes place only in the presence of living connective-tissue cells and then only after a considerable latent period. It fails entirely when the oxygen is replaced by nitrogen or hydrogen. It also fails when the tissue fragments have been heated for five minutes at 60° C. *In other words, it is evident that clot contraction is a phenomenon instituted by conditions quite different from those of primary clotting and it is a phenomenon which is brought about by the action of the products of metabolism of the connective tissue cells.*

At another time the author studied more carefully the properties of the connective tissue cells. He has found that the cells of higher animals are not highly organized, but fluid-like systems. Their various manifestations of life such as movement, growth, etc., are differential surface tension phenomena under the control of a specifically organized environment. The food materials or energy producing substances in the cultures are not derived from the medium, but from the cells within the fragment. The growth that one observes in the cultures is none other than a simple transfer of materials from the cells of the center of the fragment or in a less favorable environment to those on the periphery or those which have been carried out into the medium through the interchange of substances between the fragment and the medium. This was shown by the fact that the cells can be grown in simple salt solution and, in the plasma cultures, growth ceases after a few transplants, the sum of the total growth being less than the original mass—or it represents what one might assume to be the original mass minus the energy of transfer. The cells that tend to break down in the fragment and lead to the greater growth of the connective tissue cells are not the connective-tissue cells but the epithelium, muscle cells, etc.

Again it was noticed that this growth takes place only in the presence of oxygen. It commences after a given latent period in the case of connective tissue, subsequently to the contraction of the clot. The cells grow actively for a time, gradually to come to rest. This reaction is one which apparently commences subsequently to the slow diffusion of substances between the fragment and the medium and proceeds until an equilibrium is established In other words, it follows the curve of reaction of a heterogeneous physico-chemical system. The cells at the end of this reaction do not undergo, at least for a considerable time, any further change. They show no immediate disintegration. That this cessation of growth is not due to the exhaustion of oxygen or food materials is further shown by the failure of any change in the cells following the introduction of fresh air into the culture chamber, and by the fact that activity is again seen when the cells are transplanted to a new culture medium. On the other hand, that it is due to the accumulation of waste products is shown by the fact that the cells which tend to survive for the longer periods of time are invariably those cells which have grown out into the clot and have become completely surrounded by the contracted fibrin. It was of general interest in making these observations to note that this equilibrium which had been established in the tissue culture did not alone concern the cells which had migrated out and grown in the culture medium, but likewise those which remained within the fragment. With the cessation of growth of cells in the outer medium, disintegration with the liberation of energy-producing substances in the fragment also ceases. This is especially true when the fragments have

been placed in thick layers of plasma, so that they have become likewise completely surrounded by contracted clots. Many such cultures were kept for as long as six months at incubator temperature and in an ample supply of oxygen before any disintegration became apparent. Several were transplanted at this time and an active growth of cells was observed. The growth of the connective-tissue cell is apparently a tissue and not a cellular reaction. The failure of the connective-tissue cells to dissolve the fibrin and their ability to transform it into fibrils, leads to the belief that these fibrin fibrils form the superstructure upon which, or out of which, the connective-tissue fibrils are built. We observed pink-staining fibrils only in cultures of skin of foetal chickens. Whether the formation of the connective-tissue fibril is a body, rather than a connective-tissue cell reaction, is a question for solution.

It is well known that the growth of cells in the animal organism is not determined alone by food and oxygen but by other unknown conditions. The question naturally arises: Have these unknown conditions been found? Are the actual waste products of metabolism of these cells substances which are insoluble in body fluids; and is the cessation of growth of a part the result of the accumulation of these substances? One may asume that the fibrin fibrils are formed by the action of the products of metabolism of connective-tissue cells on the coagulable exudate, and that the cessation of growth in the wound is due to the accumulation of these substances in and about the growing cells. From these observations, one might readily define stimulation as any condition which would lead to the reduction of concentration in these substances. The stimulating action of fibrin is due to its ability to absorb these substances. To prove this more completely the author studied rhythmical activity in heart muscle cells as well as the growth of these and of connective-tissue cells in plasma cultures so arranged that the media could be continuously washed with a stream of serum. The rhythm of heart muscle fragment in simple hanging drop cultures is invariably intermittent. In the body it is a form of activity which continues throughout the life of the individual. In the cultures, where the medium was continuously washed by a stream of serum, the rhythm was not only greatly prolonged up to the time of complete exhaustion of the cells but it continued regular, while the growth of the cells was not changed but similar to that seen in the simple hanging-drop cultures. In a former paper before this society, the author presented facts to show that the contracting, embryonic heart-muscle cell has an organization which one might readily assume capable of splitting these insoluble waste products into simpler substances and of transforming the energy liberated with their formation into work of contraction.

Certain rapidly growing tissues, such as embryonal and rapidly growing tumors, grow readily in liquid media. This growth takes place only near the surface of the liquid. Cells suspended in liquid invariably round off and show no activity. The cells do not grow out into the liquid. It is of interest to note that adult tissues do not, however, grow readily in liquid media, whereas, on the other hand, they grow actively in plasma.

It was in the light of these facts and the more careful study of the properties of epithelia as well as leucocytic and lymphocytic cells that the general deductions as to the cause of the failure of scar formation in superficial inflammations of the epithelial surfaces were derived. Epithelial cells invariably bring about a rapid dissolution of the fibrin clots. When occurring in considerable numbers in a fragment of tissue, they invariably prevent entirely a growth of the connective-tissue cells. That the appearance of organization in the pneumonic lung probably indicates a complete destruction of the epithelium rather than the lack of leucocytes in the exudate was further suggested by the fact that the leucocytic infiltration in deep-seated inflammations is frequently as great as in the superficial ones. It is true that the leucocytes of man are richer in ferments than those of lower animals; the failure to observe any extensive liquefaction about the leucocytes of chickens would not indicate that this did not occur in human beings. On the other hand, it has been found that fragments of human connective tissue containing leucocytes grow readily in plasma clots when they are removed after 24 hours from the first culture to a drop of fresh plasma. This is not true of epithelium. The cells continue to liquefy the plasma even after many transplants, or until they are dead.

These observations are reported not only for the general bearing that they have on the nature of stimulation and the significance of extracellular substances in their relation to life processes, but also for their immediate significance for the better understanding of the actual conditions which regulate the growth of body cells. If these experiments are substantiated, showing, as it is believed they do, that growth is inhibited by the accumulation of insoluble waste products and permitted to proceed only by their removal, then the problem of the growth of the cell is brought into the domain of chemistry. Thus problems, such as those that confront us in cancer, are narrowed.

TRANSFUSION OF BLOOD BY THE CITRATE METHOD.

By V. P. W. SYDENSTRICKER, M. D., V. R. MASON, M. D., and T. M. RIVERS, M. D.

(Abstract of article in Jour. Am. Med. Ass., 1917, LXVIII, June 9.)

Transfusion of blood has been made simple by the use of anticoagulants, the citrate of soda having been shown to be the best and the least toxic. Two grams of sodium citrate given intravenously often cause chilly sensations and fever. However, in transfusion work two grams are practically never given at one time, as blood can be kept fluid by 0.25 per cent.

Donors should be carefully selected and all transmissible diseases excluded. A Wassermann test should be done on the donor's serum, if time permits. If cardiacs are used, a bacterial endocarditis should be excluded by blood culture if necessary. Malaria should be guarded against by the history and an examination of the blood.

After a healthy donor has been secured, agglutination tests should be properly carried out. This is done by mixing a drop each of the donor's serum and of the recipient's corpuscles suspended in physiological salt solution, and *vice versa*, and

incubating them for one hour at 37° C. Agglutination may take place quickly, but some severe reactions may be avoided if all tests are allowed to stand a full hour.

Human bloods fall into four groups, and group IV corpuscles (Moss) are not agglutinated by any other group's serum. Consequently group IV blood can be given to anybody without risk of a severe reaction. Nevertheless, it is better to centrifuge the citrated blood, pipette off the serum and make back to volume with physiological salt solution before giving.

The technic of citrate transfusion is very simple. The procedure can be carried out anywhere by one person if necessary, and the blood can be kept on ice for a number of hours without danger. The blood is drawn from the donor's median basilic vein by light suction into a graduated bottle, the citrate solution being mixed gradually by being run in through a graduated separating funnel. Ten cubic centimeters of 2.5 per cent sodium citrate solution will keep 90 c. c. of drawn blood from coagulating. After the blood has been drawn, it is transferred to an infusion bottle or salvarsan apparatus and run into the recipient's median basilic vein.

Since the introduction of the citrate method into this hospital, 34 patients have received a total of 100 transfusions. The procedure has been carried out in a variety of conditions, as pernicious anæmia, secondary anæmia, burns, leukæmia, sepsis, typhoid fever and uræmia. The indications and results are similar to those that have been reported by other authors using the older methods.

Reactions after transfusions of all kinds are very interesting. Some are certainly due to carelessly performed agglutination tests, but others occur when the bloods match perfectly by the routine tests. As the question of reactions after repeated transfusions and often after the first transfusion of compatible blood is very interesting and little understood, the remainder of the abstract will be taken directly from the original paper:

The symptoms following transfusion of blood are in order of frequency malaise, slight elevation of temperature, chilly sensations, actual rigor, urticaria, pruritus, nausea, vomiting, lumbar pain, dyspnœa, cyanosis and hæmoglobinuria. Any single one or combination of these symptoms occurring within three hours after transfusion has been considered a reaction. Such symptoms have been present in 17 per cent of the cases reported. Most of the reactions were trivial, none was fatal. In every case the bloods were compatible by the routine tests.

The cause of these reactions is not definitely known. Typical anaphylactic-like reactions of mild grade are not uncommon and are quickly relieved by a hypodermatic injection of adrenalin. Three followed the transfusion of washed cells. One occurred in a patient with typhoid fever, following transfusion from a convalescent typhoid patient. Garbat has observed slight chills and some elevation of temperature following the intravenous injections of 2 grams of sodium citrate. In none of these cases has more than 1.75 grams of citrate been used. This quantity would hardly account for the symptoms. The reactions seem to bear no relation to the volume of the transfusion, many having followed small ones.

In this connection two cases of pernicious anæmia are of some interest. Mrs. J. B. received 9000 c. c. of blood by the Lindeman method between December 10, 1915, and February 14, 1916, without any severe reactions. During this admission her spleen was removed. She was readmitted in August, 1916, with extreme anæmia. Citrate transfusions from her husband and brother (each had been the donor several times previously) were followed by severe, almost fatal, reactions with hæmoglobinuria. A Lindeman transfusion, from a new donor, was followed by chill, high fever, coma and death. There were marked hæmoglobinuria and hæmoglobinemia. The case of H. A. P. is similar in many respects. Splenectomy and repeated transfusions had been performed during previous admissions. Following a citrate transfusion from a previous donor he had a severe reaction, chill, stupor and hæmoglobinuria. A new donor was secured, but a similar reaction followed. No more transfusions were attempted.

These two cases have suggested the possibility of the formation, after repeated transfusions, of antibodies to homologous blood which are not demonstrable *in vitro*. In both after the occurrence of severe reactions, tests were done with particular care. Gross and microscopic preparations were made with varying dilutions of the donor's and recipient's sera. These were incubated one hour at 37° C., then put on ice for 24 hours and again incubated. There was no agglutination or hemolysis. Similar tests were done in the choosing of subsequent donors with negative results, yet transfusion from these donors gave most severe reactions. Without attempting to explain these, it would seem that transfusion is a self-limited method of treatment in pernicious anæmia, since after a certain number of transfusions homologous blood may cause reactions of increasing severity. We have been unable to produce any similar result experimentally in normal animals.

SURFACE STERILIZATION OF TISSUE FOR BACTERIAL STUDIES.

By D. M. Davis, M. D., and Robert Rosen.

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(Abstract. To appear in full in the Journal of Infectious Diseases shortly.)

In a series of experiments for the purpose of studying the bacterial content of the prostate, certain difficulties were encountered with the methods commonly described for making cultures from tissues. It was found that by using the method recommended by Rosenow certain discrepancies occurred in the results which suggested that they may have been due to contamination introduced at some point between the time the tissue was exposed by the surgical scalpel and the final closure of the culture tube. In order to decide this question decisively it was determined to put a close check on each step in this process.

Grinding up glandular tissues in a sterile mortar, flaming the tissues, dipping them in boiling saline, water or hot oil, were methods used by previous investigators. The time element varies with the size of the tissues used. Owing to the

fact that the air-chamber recommended by Rosenow, as found on the market, is not air-tight, that it is very unstable, that only one hand can be introduced and that the large cotton plug used is difficult to manage, it was decided to design a new chamber to eliminate these difficulties. The chamber, as finally constructed, is made of heavy tin with large panes of plate glass at both the top and front, a handhold at each end, to which canvas gloves are attached, so that both hands can work on the inside of the box, and an opening on the metal side for introducing the necessary materials and tissue. The flange of this opening is one-fourth inch smaller than the cap, so that the edge of the cap never comes in contact with the flange. This eliminates the cotton plug.

The apparatus was tested out for its sterility by placing in it tissue which had been autoclaved, its surface later inoculated with Staphylococcus aureus and again sterilized by the methods to be described. The hands were rendered relatively sterile and non-bactericidal, inoculated with *B. violaceus*, inserted into the canvas gloves attached to the chamber and the tissue was cut up and ground for 30 minutes, poured into a test tube and removed from the chamber, and plated, 1 c. c. per plate being used. In this process the sterile broth and the tissue were the only articles introduced into the chamber after the chamber had been sterilized. In 12 such experiments the plates remained sterile.

Having eliminated the dangers of contamination from the chamber the methods of surface sterilization of tissues to be used in bacterial study had to be checked up. For this autoclaved tissue was inoculated superficially or deeply with Staphylococcus aureus.

Outline of Method.

1. Mortars or evaporating dishes and pestles, scissors and tissue forceps are placed in a wire basket and sterilized in the hot-air oven for one hour at 190° C., the mortars or dishes being upside down.

2. Autoclaved kidney or liver is placed in a sterile glass jar containing tissue forceps and scissors, and cut into pieces about 1.5 x 2 x 1.5 cm. in size.

3. A piece of tissue is immersed in an emulsion of a 24-hour broth culture of the organism for an instant.

4. The tissue is placed in hot liquid paraffin, boiling saline or passed through a bunsen flame for the desired length of time.

5. It is removed to a sterile mortar, in which are 10 c. c. of sterile bouillon, and ground with the sterile pestle.

6. One cubic centimeter of this tissue emulsion is removed and plated. The procedure is repeated, the time of heating and media being changed as desired.

7. As a check on the tissue used, a piece which has not been inoculated is emulsified and 1 c. c. of this emulsion is plated.

8. As a check on the organism and to have a culture where no sterilizing methods have been used with which to compare the growth from the heated tissue, a piece of tissue is dipped in a bacterial emulsion and run through just as is done to the pieces which have been heated.

9. For deep tissue inoculation a hypodermic syringe is used, the bacterial emulsion being forced into the interior of the tissue and the whole then dipped in the same emulsion. The procedure from this point is the same as above. In this way the amount of heat necessary to destroy the surface bacteria without interfering with the organisms that are on the interior could be determined.*

Discussion.

1. The time required for surface sterilization by the boiling salt solution was found to be 25 seconds, which is sufficient to sterilize the tissue throughout, giving no margin of safety.

2. The same was true for the sterilization by the bunsen flame method, the required 25 seconds being sufficient to char the tissue.

3. For liquid paraffin, at 180° C., the thermal death point was below 10 seconds for surface sterilization. This is not sufficient to destroy bacteria on the interior which requires 20 seconds. Ten seconds seemed to be sufficient for surface sterilization, leaving a wide margin of safety. In the case of a thermosensitive organism the time and temperature factors might have to be varied.

Summary.

1. With the air chamber and technique described in this paper, danger of contamination from the outside during the making of cultures from tissues is reduced to the minimum.

2. It is apparent that the boiling water method as formerly used is inadequate for surface sterilization, and that the time required to sterilize the surface with certainty approaches that sufficient to sterilize the gland completely.

3. The same objections apply to the bunsen flame; the flame either does not reach every part of the tissue or the charred tissue acts as a non-conductor of heat.

4. The hot oil method of sterizilation answers the purpose better than the preceding two methods, inasmuch as at a temperature of 180° C., surface bacteria will be destroyed in 10 seconds without any apparent interference with the organisms in the interior of the tissue, which are not killed unless it is heated for 20 seconds.

5. In view of the stress laid on the bacteriology of glandular tissues in relation to the etiology of disease, it becomes apparent at once that surface sterilization is of the utmost importance. Having obtained a satisfactory method of surface sterilization, more confidence can be placed in the results obtained in future studies.

*** It is understood that this is an exaggeration of the infection usually present on tissues to be cultured, but that such infection is not negligible is shown by a recent culture of 10 c. c. of broth into which a piece of prostate, dropped by the operator into a sterile glass jar, had been placed for a moment. A plate made with 1 c. c. contained 250 colonies. In another case, 1 c. c. of broth in which the prostate had been immersed produced 250 colonies, whereas after immediate surface sterilization for eight seconds in liquid paraffin at 180° C., emulsifying the tissue in which a pus cavity was found and plating 1 c. c. of this emulsion, the colonies were innumerable.**

NOTES ON NEW BOOKS.

The Kinetic Drive. By GEORGE W. CRILE, M. D. Wesley M. Carpenter Lecture, 1915. Illustrated. 8 vo. 71 pages. Cloth, $2.00. (*Philadelphia and London: W. B. Saunders Company, 1916.*)

Man—An Adaptive Mechanism. By GEORGE W. CRILE, M. D. 8 vo. 387 pages. Cloth, $2.50. (*New York: The Macmillan Company, 1916.*)

The second of these books gives a fuller presentation of essentially the same topic of which the first book treats in a more summary and more pointed manner. The documentary material is to appear in a full account of the researches from which the illustrative material has been drawn. Strictly speaking, both works represent the formulation of the personal philosophy of one of our foremost surgeons. It is an emphatic appreciation of the functional-mechanistic view of man in action, a view of life as a drive, a struggle, a battle, with an interest in the rôle of physics and chemistry as keen and unrelenting as the interest in heredity and selection shown in Darwin and his followers. We might speak of a revival of Darwinian philosophy with emphasis on the conquests of modern physiology. In all the facts of anatomy and physiology— "in the complete life cycle of the individual from conception to death we see clearly here and dimly there the mechanisms by means of which a sensitive being immersed in a hostile environment effects survival—we see man—an adaptive mechanism." War and struggle seem to dominate. "In understanding the physical basis of the action of faith and hope, as opposed to fear, despair, anger and grief, we have at our command a concrete force which can be efficiently used to protect the individual. As the knowledge of disgrace and punishment prevents dishonesty; as the knowledge of contagion prevents exposure to contagion, so the mere knowledge—the conviction—that excessive anger, work, jealousy, envy, worry or grief cause physical damage as serious as that produced by infections or crushing blows will constitute a powerful protection to man. The knowledge that these activations not only decrease the power of the individual to do his work, but ultimately cause numerous diseases as well, will result automatically in arousing the instinct of self-preservation, which will surround the individual with a protecting circle, through which anger, jealousy, grief, and worry cannot penetrate, just as the zone of local anesthesia in the anociated surgical operation is an impenetrable barrier between the brain and the knife, making the surgical operation shockless."

The striking feature of this intensely dynamic conception is Crile's willingness to give prominent attention to the emotions. The author's interest in surgical shock and the obviously intense interest in Darwinian philosophy and, we may infer, a keen feeling against non-biological conceptions, have led him to the formulation of a Kinetic System, with the brain as the initiator and driver, the adrenals as the "oxidizers, making possible the transformation of energy and the neutralization of the resulting acid products," the liver as fabricator and storehouse of fuel, the muscles the transformers of energy into heat or motion, the thyroid the organ of speed control through facilitation of the passage of ions. With this goes the interest in a uniform explanation of "acute activation of the organism by infection, by foreign proteins, by exertion, by emotion, and by physical injury." "As our evidence has accumulated, we have come to see that more of the chronic diseases result from the *excessive work thrown upon certain organs for the elimination of the superabundant acid products of energy transformation than result primarily from the energy transformation itself*" (p. 10). "The *kinetic drive* harmonizes many facts in the great clinic of life as well as in the restricted clinics of medicine; it emphasizes the value of a mechanistic view of life in the study of both normal and pathologic processes; and it suggests a philosophy of life by means of which self-preservation may be secured through kinetic control." This control can be attained by guarding against overstimulating factors, by the substitution of hope for fear, by narcotics, and possibly even by the reducing in size of the activating organs, the adrenals and thyroid —by a "dekinetizing" operation.

There is hardly a doubt that a strongly individual positive revulsion against anti-mechanistic and non-dynamic views of life and attitudes in medicine finds its expression in these books. They deal with the push and drive of life and urge upon the physician to heed the importance of emotion as well as of other factors in life, and to make the assimilation acceptable, the mechanistic presentation of the many factors to be considered is sought as the general solution.

The work is very personal. There is little effort to assimilate the material and discussions of other investigators and thinkers or to point out the author's relation to other viewpoints. The foundation for the claims are largely furnished by the physiological and histological researches of Crile's clinic and laboratory. The one difficulty for other workers in dealing with Crile's facts lies in Crile's tendency to argue from extreme results and observations which might be open to more than one interpretation and would not necessarily form a sound foundation for the rank and file of experience. The histological pictures of the cerebellum in my own series of unselected but well controlled observation tend to convince me that they do not form as striking an index of the status of the whole organism as Crile's account might suggest. The extension of the study to less extreme degrees of change will make it clear that other *functional* methods cannot be dispensed with. And with this broadening out, it may well be that there will be space for less extreme mechanistic conceptions for a physician's philosophy.

The great value of the two books lies in the vigorous effort at functional formulation of human problems. They present a forceful plea for a reanimation of medical science. Science has to sum up its facts and outlooks occasionally. Even if Crile's claims in detail should not stand and the extreme cautions of "anociated surgical operation" might not be so strictly called for, Crile has succeeded in reintroducing some consideration for emotions, and he is paving the way for a wider interest in Cannon's work and other modern contributions. That one has a feeling of too much being promised in a simple scheme, and that through such simple solutions the patience with the really needed more complicated types of work and conceptions might suffer, need not detract from Crile's service to medical thoughtfulness. Some workers are driven by enthusiasm, others more by a stubborn critical determination. The mutual and frank discussion of the two types will bring us further than extreme perfectionism and conservatism.

Surgery in War. By ALFRED J. HULL, F. R. C. S., Major, Royal Army Medical Corps; with a Preface by SIR ALFRED KEOGH, K. C. B., M. D., Director-General Army Medical Service. Cloth, $4.00. Pp. 390, with 81 illustrations. (*Philadelphia: P. Blakiston's Son & Co., 1916.*)

The present war has given surgeons and sanitarians wonderful opportunities for observation. This little book is a compilation by Major Hull of several articles on various phases of war surgery. The authors are all members of the British Medical Corps and men of renown. The arrangement is logical and the discussions are, on the whole, clear and complete. There is, however, some tendency to repetition, particularly in the matter of the new irrigation treatment of wounds.

The book would be of much more scientific value if it contained statistics. The author apologizes for this defect and lays the blame on the censor.

H. R. S.

BOOKS RECEIVED.

The Medical Clinics of Chicago. Vol. II, No. 2, September, 1916. 8°. 417 pages. W. B. Saunders Company, Philadelphia and London.

Studies in Blood Pressure, Physiological and Clinical. By George Oliver, M. D., Lond., F. R. C. P. Edited by W. D. Halliburton, M. D., F. R. S. Third edition. 1916. 8°. 240 pages. Paul B. Hoeber, New York.

Practical Bacteriology, Blood Work and Animal Parasitology, Including Bacteriological Keys, Zoological Tables and Explanatory Clinical Notes. By E. R. Stitt, A. B., Ph. G., M. D. Fourth edition, revised and enlarged. 1916. 12°. 497 pages. P. Blakiston's Son & Co., Philadelphia.

Burdett's Hospitals and Charities, 1916. Being the Year Book of Philanthrophy and the Hospital Annual. By Sir Henry Burdett, K. C. B., K. C. V. O. Twenty-seventh year. 1916. 12°. 1070 pages. The Scientific Press, Limited, London.

American Proctologic Society. Transactions of the Eighteenth Annual Meeting. 1916. 8°. 144 pages. Printed by The Proctologist, St. Louis, Mo.

Applied Immunology. The Practical Application of Sera and Bacterins Prophylactically, Diagnostically and Therapeutically; with an Appendix on Serum Treatment of Hemorrhage, Organotherapy and Chemotherapy. By B. A. Thomas, A. M., M. D., and R. H. Ivy, M. D., D. D. S. Five colored inserts and 68 illustrations in the text. Second edition revised. 1916. 8°. 364 pages. J. B. Lippincott Company, Philadelphia and London.

Pharmacology and Therapeutics. For Students and Practitioners of Medicine. By Horatio C. Wood, Jr., M. D. Second edition. 1916. 8°. 455 pages. J. B. Lippincott Company, Philadelphia and London.

A Text-Book of Practical Therapeutics, with Especial Reference to the Application of Remedial Measures to Disease and their Employment upon a Rational Basis. By Hobart Amory Hare, M. D., B. Sc. Sixteenth edition, enlarged, thoroughly revised, and largely rewritten. Illustrated with 149 engravings and seven plates. 1916. 8°. 1009 pages. Lea & Febiger, Philadelphia and New York.

Three Contributions to the Theory of Sex. By Prof. Dr. Sigmund Freud, LL. D. Authorized Translation by A. A. Brill, Ph. B., M. D. With Introduction by James J. Putnam, M. D. Second revised and enlarged edition. Nervous and Mental Disease Monograph Series No. 7. 1916. 8°. 117 pages. Nervous and Mental Disease Publishing Company, New York.

The Significance of Psychoanalysis for the Mental Sciences. By Dr. Otto Rank and Dr. Hanns Sachs. Authorized English translation by Dr. Charles R. Payne. Nervous and Mental Disease Monograph Series No. 23. 1916. 8°. 127 pages. Nervous and Mental Disease Publishing Company, New York.

Manual of Chemistry. A Guide to Lectures and Laboratory Work for Beginners in Chemistry. A Text-Book Specially Adapted for Students of Medicine, Pharmacy and Dentistry. By W. Simon, Ph. D., M. D. and Daniel Base, Ph. D. Eleventh edition, thoroughly revised. With 55 illustrations, one colored spectra plate and six colored plates representing 48 chemical reactions. 1916. 8°. 648 pages. Lea & Febiger, Philadelphia and New York.

Mechanisms of Character Formation. An Introduction to Psychoanalysis. By William A. White, M. D. 1916. 8°. 342 pages. The Macmillan Company, New York.

Royal College of Surgeons of England. Calendar, August 1, 1916. 8°. 407 pages. Taylor & Francis, Red Lion Court, Fleet Street, London.

Syphilis. By Loyd Thompson, Ph. B., M. D. Illustrated with 77 engravings and seven plates. 1916. 8°. 515 pages. Lea & Febiger, Philadelphia and New York.

Blood Pressure, from the Clinical Standpoint. By Francis Ashley Faught, M. D. Second edition, thoroughly revised. 1916. 8°. 478 pages. W. B. Saunders Company, Philadelphia and London.

Constipation, Obstipation and Intestinal Stasis (Auto-Intoxication). By Samuel Goodwin Gant, M. D., LL. D. Second edition, enlarged with 259 illustrations. 1916. 8°. 584 pages. W. B. Saunders Company, Philadelphia and London.

University of Sydney. Calendar of the University of Sydney for the Year 1916. 8°. 695 pages. Angus & Robertson, Ltd., Sydney.

Royal Academy of Medicine in Ireland. Transactions. Vol. XXXIII, 1915, 465 pages and Vol. XXXIV, 1916. 288 pages. Edited by J. Alfred Scott, M. A., M. D., F. R. C. S. I. 8°. John Falconer, Dublin; Baillière, Tindall & Cox, London; James Thin, Edinburgh; John Wright & Co., Bristol.

United States. Department of Commerce. Bureau of the Census. Sam. L. Rogers, Director. Mortality Statistics, 1914. Fifteenth Annual Report. 1916. 4°. 714 pages. Government Printing Office, Washington.

United States. Department of Commerce. Bureau of the Census. Sam. L. Rogers, Director. Financial Statistics of States, 1915. 1916. 4°. 125 pages. Government Printing Office, Washington.

Studies from the Rockefeller Institute for Medical Research. Reprints. Volume XXV. 1916. 8°. 583 pages. The Rockefeller Institute for Medical Research, New York.

The National Association for the Study and Prevention of Tuberculosis. Transactions of the Twelfth Annual Meeting. 1916. 8°. 517 pages. The National Association for the Study and Prevention of Tuberculosis, New York.

A Text-Book of Organic Chemistry. For Students of Medicine and Biology. By E. V. McCollum, Ph. D. 1916. 16°. 426 pages. The Macmillan Company, New York.

Materia Medica for Nurses. By A. S. Blumgarten, M. D. Second edition, completely revised, with additions and new illustrations. 1916. 8°. 651 pages. The Macmillan Company, New York.

The Pathology and Differential Diagnosis of Infectious Diseases of Animals. Prepared for Students and Practitioners of Veterinary Medicine. By Veranus Alva Moore, B. S., M. D., V. M. D. Fourth edition revised and enlarged with 120 illustrations. 1916. 8°. 593 pages. The Macmillan Company, New York.

Report of the First Expedition to South America, 1913. Members of the Expedition Richard P. Strong, Ernest E. Tyzzer, Charles T. Brues, A. W. Sellards, J. C. Gastiaburu. Harvard School of Tropical Medicine. 1915. 4°. 220 pages. Harvard University Press, Cambridge.

United States. Navy Department. Bureau of Medicine and Surgery. Annual Report of the Surgeon General, U. S. Navy, to the Secretary of the Navy. For the Fiscal Year 1916. 8°. 104 pages. Government Printing Office, Washington.

United States. Public Health Service. Annual Report of the Surgeon General of the Public Health Service of the United States. For the Fiscal Year 1916. 8°. 421 pages. Government Printing Office, Washington.

American Surgical Association. Transactions. Volume XXXIV. Edited by John F. Binnie, M. D. 1916. 8°. 540 pages. William J. Dornan, Philadelphia.

Teacher's Guide for Blumgarten's Materia Medica for Nurses. By A. S. Blumgarten, M. D. 1916. 8°. 16 pages. The Macmillan Company, New York.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. By leading members of the medical profession throughout the world. Edited by H. R. M. Landis, M. D. Volume IV. Twenty-sixth series. 1916. 8°. 307 pages. J. B. Lippincott Company, Philadelphia and London.

Notes on the Causation of Cancer. By the Hon. Rollo Russell, with a Preface by Dr. Dawtrey Drewitt. 1916. 12°. 116 pages Longmans, Green & Co., London.

The Rockefeller Foundation. Annual Report, 1915. [1916.] 8°. 377 pages. Published by the Rockefeller Foundation, 61 Broadway, New York.

Cardio-Vascular Diseases. Recent Advances in their Anatomy, Physiology, Pathology, Diagnosis and Treatment. By Thomas E. Satterthwaite, A. B., M. D., LL. D., Sc. D. 1913. 8°. 166 pages. Lemcke and Buechner, New York City.

Bellevue and Allied Hospitals. City of New York. Fourteenth Annual Report, January 1, 1915 to December 31, 1915. 8°. 157 pages. New York City.

My Birth, the Autobiography of an Unborn Infant. By Armenouhie T. Lamson. 1916. 12°. 140 pages. The Macmillan Company, New York.

Public Health Nursing. By Mary Sewall Gardner, R. N. With an Introduction by M. Adelaide Nutting. 1916. 12°. 372 pages. The Macmillan Company, New York.

The Animal Parasites of Man. By H. B. Fantham, M. A. Cantab., D. Sc., Lond., J. W. W. Stephens, M. D. Cantab., D. P. H. and F. V. Theobald, M. A. Cantab., F. E. S., Hon. F. R. H. S. Partly adapted from Dr. Max Braun's "Die Tierischen Parasiten des Menschen" (4th Edition, 1908), and an Appendix by Dr. Otto Seifert. 1916. 8°. 900 pages. William Wood & Co., New York.

American Gynecological Society. Transactions. Volume XLI, for the year 1916. 8°. 726 pages. William J. Dornan, Philadelphia.

Cornell University Medical Bulletin. Volume VI, Number 2, October, 1916. Studies from the Department of Medicine including Applied Pharmacology and Dermatology. 8°. 355 pages. Published by Cornell University, New York City.

Interstate Commerce Commission. Thirtieth Annual Report. 1916. 8°. 248 pages. Government Printing Office, Washington.

AN APPEAL TO THE MEDICAL PROFESSION OF THE UNITED STATES.

The Surgeon General's Office has appealed to the medical press of this country for aid in securing the quota of physicians necessary for the care of the great army now in course of organization.

The Medical Departments of the Government are responsible for the examination of the recruits, the hygiene of camps and the care of the sick and wounded. The Surgeons General have not as yet been given full authority and the means to meet this responsibility.

The President and Congress can give the Surgeons General full authority and ample means, but except by the draft neither the President nor Congress is able to give them a sufficient number of men from the medical profession, as it is a volunteer service. Consequently, if the Medical Departments are furnished with the authority and the means, they will still be unable to do their work unless the medical profession of the country, and particularly the younger men, respond more freely than they have done up to this time.

In the army hospitals and first aid work abroad, in the vast concentration camps so soon to be organized in this country, and in every branch of the naval service there is an urgent demand for each physician who can and will offer his services. In the work our country has pledged itself to do, the need for doctors is imperative. Estimates give the figure of 20,000 physicians as the minimum number necessary for this work. Only about 6000 are at present enrolled. These figures speak for themselves.

Commissions in the Medical Reserve Corps are accorded on the basis of First Lieutenant, Captain and Major, with respective salaries of $2000, $2400 and $3000 a year. Applicants may apply directly to the various examining boards throughout the different states and complete all preliminary arrangements without reference to the Surgeon General's Office. The completed papers should be forwarded directly to the Surgeon General by the president of the examining board. A complete set of papers must contain the physical examination, report of the examiner as to mental, moral and physical qualifications, a personal history form filled out by the applicant and sworn to before a notary, and a certificate of state registration (except where this year's graduates have not had time to take their State Board examination). Two letters should also be sent certifying as to citizenship and moral qualifications, and if of alien birth, a certificate of naturalization.

Further information may be obtained from the State and County Committees of National Defense, or directly from Surgeon General W. C. Gorgas, of the Army, or Surgeon General W. C. Braisted, of the Navy, Washington, D. C.

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